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The Total Synthesis of the Lolium Alkaloids

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APPROVAL PAGE

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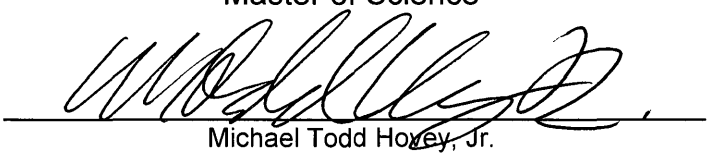

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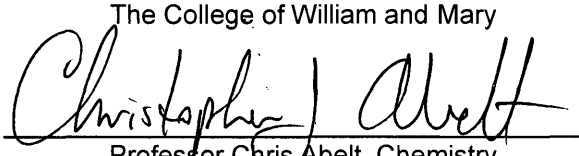

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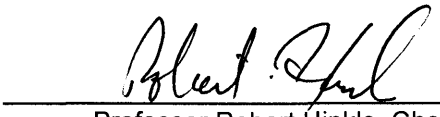

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ABSTRACT PAGE

The total synthesis of the lolium alkaloids is presented. Loline alkaloids exhibit a strained ether-bridged pyrrolizidine skeleton and possess insecticidal and insect antifeedant properties. Specifically, synthesis of acetylnorloline, a prototypical member of the loline family, is described. Central to the route is a stereoselective tethered aminohydroxylation (TA) of a homoallylic carbamate. Allylic (A1,3) strain is exploited to enforce diastereofacial selectivity during the aminohydroxylation. Studies directed toward the asymmetric synthesis of the lolines are reported as well.

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DEDICATION

For my parents Carolyn and Michael Hovey and for Ms. Juliet Sabol, without whose support this thesis would not have been possible

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THE TOTAL SYNTHESIS OF THE LOLIUM ALKALOIDS

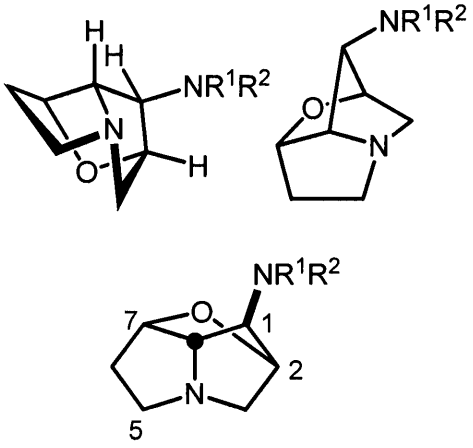
CHAPTER I

THE LOLIUM ALKALOIDS: ISOLATION, BIOSYNTHESIS AND PREVIOUS SYNTHETIC EFFORTS

Introduction:

K. C. Nicolaou has outlined four stages for the practice of total synthesis. The first stage is the selection of the target molecule.[1] Commonly, the synthetic targets of total synthesis are natural products. This thesis details the successful total synthesis of the loline alkaloids (**Table 1.1**), a class of pyrrolizidine natural products found in the *Lolium* species of ryegrasses and fescues.[2] The lolines are interesting synthetic targets because, unlike other prototypical pyrrolizidines, the lolines are characterized by a structurally unique strained ethereal bond, which bridges both rings of the bicyclic

Table 1.1: Perspective illustrations of loline alkaloids



R^1	R^2	
H	Me	**1** loline
H	H	**2** norloline
H	Ac	**3** acetylnorloline
H	CHO	**4** formylnorloline
Me	Me	**5** methylloline
Me	Ac	**6** acetylloline
Me	CHO	**7** formylloline

pyrrolizidine core as well as a pendant *exo*-cyclic amine.[3] In addition, facile synthesis of the lolines would provide ample material with which to study further their insect anti-feedant and antitumor properties.[4-6] Also, intersection of possible biosynthetic intermediates en route could answer questions about the biosynthesis of the lolines.

The second stage described by Nicolaou is the development of the synthetic route by retrosynthesis.[1,7] Past synthetic efforts toward the loline alkaloids have been unable to efficiently produce the pyrrolizidine core concomitantly with the appropriate stereochemistry required to install both the *exo*-amine as well as the strained ethereal bond.[8,9] In our route, we envisioned the installation of this key stereochemistry and functionality through application of the tethered aminohydroxylation (TA) technology developed in the laboratory of T. J. Donohue.[10] We also hypothesized that a proline derivative could act as a synthetic scaffold from which to initiate our synthesis. The final two stages outlined by Nicolaou go hand in hand; the third is the selection of reagents and reaction conditions for the forward synthesis and the fourth is the actual execution of the planned route.

Herein, all four stages are displayed for both the first generation racemic total synthesis of *N*-acetylnorloline[11] as well as the second generation asymmetric synthesis initiated from (*S*)-4-amino-2-hydroxybutyric acid, a commercially available chiral starting building block. *N*-acetylnorloline was chosen as a prototypical loline because its expedient synthesis from the loline skeleton is known.[12]

Isolation and Biosynthesis:

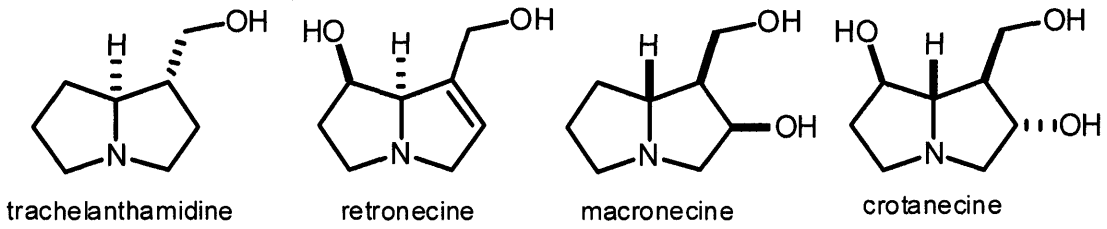
The loline alkaloids (**Table 1.1**) are a class of polycyclic pyrrolizidine metabolites from the *Lolium* species of ryegrasses and broad-leaf fescues.[3] A strained ethereal bridge between C-2 and C-7 (**Table 1.1**) as well as an *exo*-amine at C-1 typify these alkaloids.[2] Initial discovery and isolation of this specific class of alkaloids resulted from investigations into *L. temulentum*, a plant notorious among farmers for reportedly causing cattle to fall ill. Early investigations in the 1890s first reported an example of a mutualistic fungus, now known as *Neotyphodium occultans,* inhabiting the plant. In addition, a new class of metabolite compounds was discovered, which were coined the *lolium* alkaloids, named after their host species of grass.[13-15] Strangely, it was not until the late 1980s that the mutualistic relationship between the fungal endophyte and grass was conclusively reported in the literature.[2,16]

Hofmeister was the first chemist to isolate and identify a compound with the elemental formula $C_7H_{12}N_2O$ from the grass, *L. temulentum.*[15] The substance is now known as norloline (**2**, **Table 1.1**). Renewed interest in the alkaloids during the 1960s culminated in the establishment of the absolute structure of loline by Aasen and Culvenor.[17] The *exo*-1-aminopyrrolizidine-2,7-ether core was deemed characteristic of the alkaloid family.[17-22]

The lolines were originally thought to be secondary metabolites of the grasses from which they were isolated, but it was not until the work of Siegel[23] and Blankenship[24] that the lolines were conclusively shown to be specific metabolites of the symbiotic fungal endophyte. Contrary to previous disclosures, neither the lolines nor the

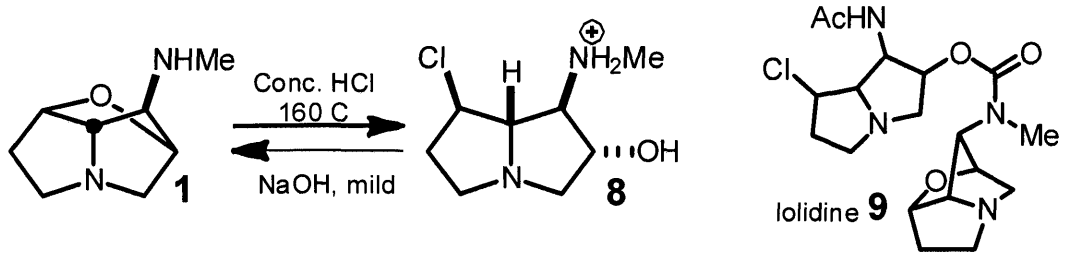
symbiotic fungus has been linked to cattle toxicosis.[2,6] In fact, the alkaloids exhibit the desirable characteristics of grass-endophyte symbiota: strong anti-insect activity which increases the survivability of both species.[2,6] Loline (**1**), the most abundant metabolite, is not only an insect anti-feedant but also exhibits modest antitumor activity.[4,5] In addition, derivatives of **1** with varied R^2 substituents possess muscle relaxant properties.[25]

Figure 1.1: Illustrative examples of prototypical pyrrolizidine natural products



The majority of pyrrolizidine natural products do not possess the strained ether bridge between C-2 and C-7 found in **1–7** (**Figure 1.1** for examples of other pyrrolizidines[26-28]). This structural peculiarity motivated exploration into the biosynthesis of the lolines. The 1960's studies into the structure of loline conducted by Yunusov and Akramov tentatively suggested a mechanism for the ether bridge formation (**Figure 1.2**).[21] Upon exposure to refluxing HCl, **1** reacted to form **8**, the chlorinated and hydroxylated derivative. Conversion of **8** back to **1** by exposure to dilute NaOH

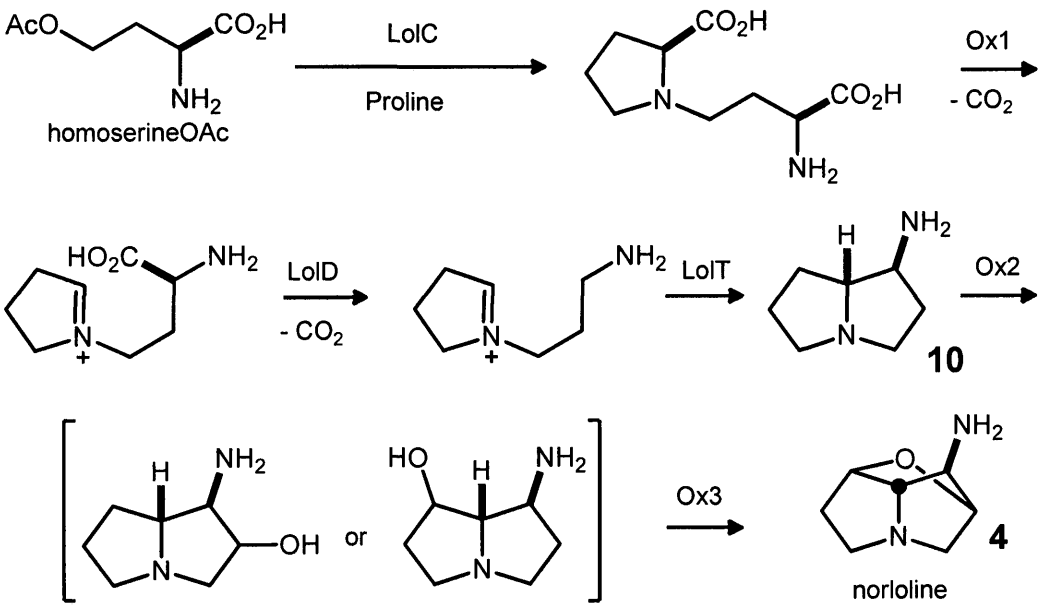
Figure 1.2: Yunusov derivatization and Batirov lolidine discovery



illustrates a possible mechanism to form the strained ether bridge. Later in 1977, Batirov and co-workers reported the structure of lolidine (**9**, **Figure 1.2**), which contains the loline core and a pendant acyl-pyrrolizidine bonded to the *exo*-1-amine of the tricycle skeleton.[29] The pendant pyrrolizidine contains chlorination at C-7 and hydroxy functionality at C-2, which is almost identical to the proposed structure of **8**, prepared by Yunusov and Akramov.[29] No definitive answers about the formation of the ethereal bond have been published to date. One of the goals of this work is to develop tools with which to determine the ethereal bond biosynthetic precursor

Initial research conducted in the early 1990s by Bush and co-workers extrapolated from the already known plant pyrrolizidine biosynthetic pathways to suggest a route for the lolines.[16] These studies were not fruitful because, as was later determined, the lolines are endophyte metabolites. Even though lolines possess a pyrrolizidine alkaloid (PA) core, the installation of the *exo*-1-amine requires biosynthetic intermediates and transformations that plant biosynthesis of the PA core does not contain.[30,31] Schardl and

Scheme 1.1: The proposed biosynthetic pathway to the lolium alkaloids



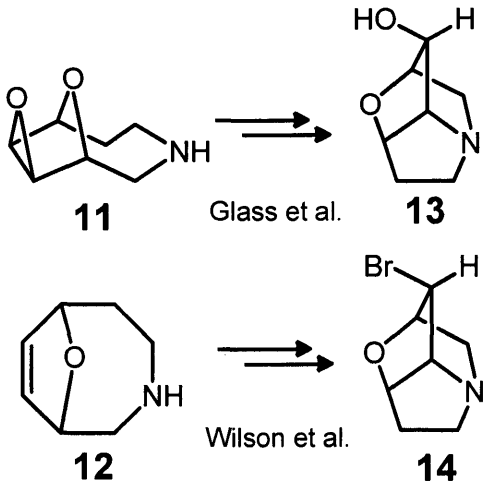
co-workers report in 2005 that the PA core is formed *via* a previously unknown, *in vivo,* γ-substitution reaction between proline and homoserine (**Scheme 1.1**).[30] In 2007, Schardl and co-workers synthesized isotopically labeled intermediate **10** as well as *L*-4-*cis*-hydroxyproline and *L*-4-*trans*-hydroxyproline for use in feeding studies.[3] These investigations determined that the PA substructure is formed before oxidation at either C-2 or C-7 (the 2 carbons of the ether bond in the loline core). This implies that the specific oxidation required to form the bridging ether bond takes place in one of the final steps of the pathway (**Scheme 1.1**).[31]

Though much progress has been made in determining the biosynthetic route to the lolines, many questions remain. The stereochemistry and structures of the intermediates that occur between **10** and **4** remain unknown. Of continued interest is the order of decarboxylation that takes place en route to **10**. Also, it is unknown if the precursor to the bridging ether bond is analogous to the PA substituent present in lolidine (**9**). The long-term goal of our synthetic efforts is to prepare compounds that can help answer these questions. Development of an expedient synthesis of the *exo*-1-aminopyrrolidine-2,7-ether loline core provides further synthetic strategies to further study the proposed biosynthetic intermediates.

Previous Synthetic Efforts Toward the *Lolium* Alkaloids:

Pyrrolizidine alkaloids (PA) have been popular synthetic targets for over half a century. Once the absolute structure of loline was established in 1972[17,18], (See **Table 1.1)** synthetic interest was piqued as evident by the number of publications towards their synthesis.[8,9,32,33] Loline proved difficult to synthesize. Two partial syntheses by Glass and co-workers in 1978 as well as by Wilson and co-workers in 1981 were reported.[32,33] In 1986, Tufariello and co-workers reported the first complete synthesis of loline, more than fourteen years after the absolute structure was determined.[9,32,33] The first asymmetric total synthesis of **1** was not achieved until 2000 by White and co-workers. [34]

Figure 1.3: Glass and Wilson syntheses



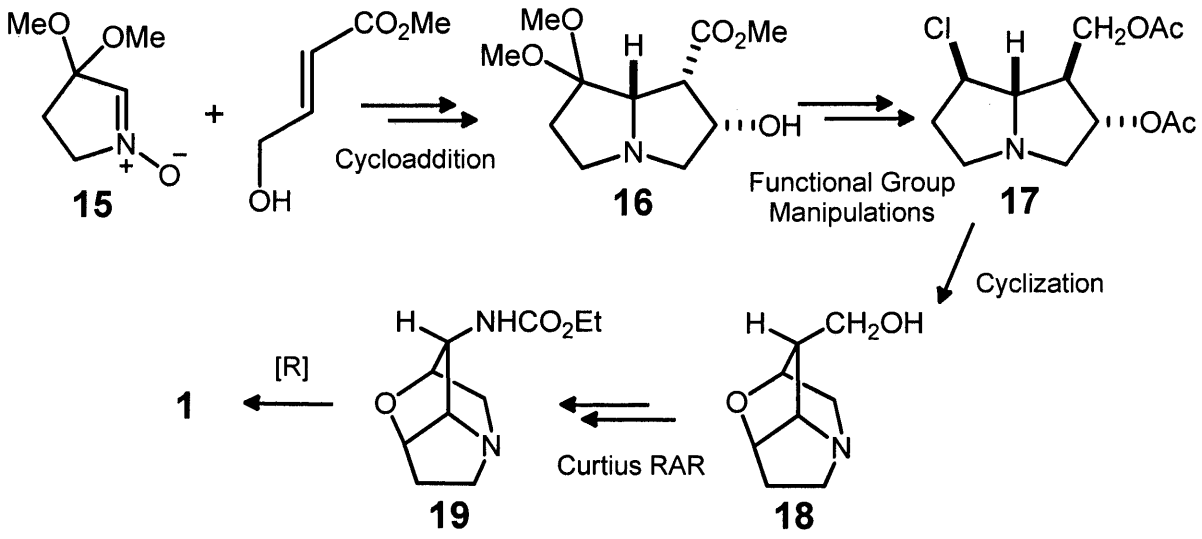
The first two partial syntheses (Glass and Wilson) highlighted a key flaw in the common synthetic strategy toward the *exo*-1-aminopyrrolizidine-2,7-ether core. Both Glass and Wilson used creative tactics to form the PA core, but failed to establish the proper stereochemistry at C-1 to provide the *exo*-1-amine functionality. Glass's strategy revolved around an intramolecular cyclization of amino epoxide **11 (Figure 1.3)** to form the tricyclic loline skeleton. By bromination of **12**, Wilson and co-woorkers wer able to

form the core structure **14** in one step as well as install a suitable bromine leaving group in the *endo*-1 position.[32]

Both groups exhaustively searched for appropriate nitrogen-containing nucleophiles to displace the *endo* (to the convex face of the pyrrolizidine bicycle) leaving groups of **13** and **14**, but neither proved productive. The research groups hypothesized that steric congestion of the polycyclic framework as well as the lone pair on the tertiary amine prevented constructive interaction between any nucleophilic HOMO and the $\sigma^*_{C\text{-}O}$ LUMO at C-1 which effectively halted S_N2 reactivity. These experiments determined the necessity of establishing the required *exo*-1-amine stereochemistry prior to formation of the PA and ether bond framework. The execution of the following syntheses proved this hypothesis correct.

The first total synthesis of the lolium alkaloids is the racemic synthesis of **1** by Tufariello and co-workers in 1986.[9] Central to their synthesis is the nitrone-based [3+2] methodolgy developed in Tufariello's labs.[35,36] The synthesis commences with a

Scheme 1.2: The racemic total synthesis of loline by Tufariello and co-workers.

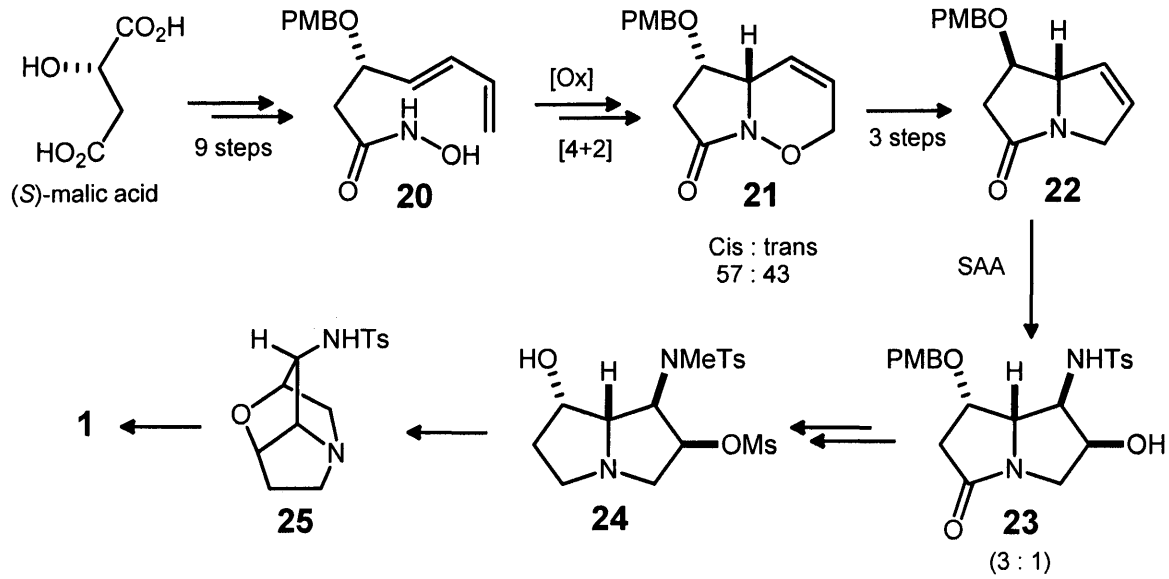


cycloaddition between nitrone **15** and methyl 4-hydroxycrotonate to form pyrrolizidine **16** (**Scheme 1.2**). The stereochemistry at C-1 is *endo* relative to the convex face of the pyrrolizidine instead of *exo* as required by the final product. Exposure to NaOMe epimerizes C-1, converting **16** to the desired *exo* configuration. Functional group manipulations finish the synthesis of substrate **17.** Saponification of acetate **17** promotes cyclization to afford alcohol **18**. Oxidation of alcohol **18** to the carboxylic acid and a subsequent Curtius rearrangement resulted in carbamate **19**. Exposure of **19** to lithium aluminum hydride yielded **1,** completing the total synthesis of loline.[37,38]

Inspection of Tufariello's route highlights key considerations for developing a concise synthesis of the lolines. In preparing **17** from substrate **16,** Tufariello found that PA *endo/exo* preference established by the concave and convex faces can be exploited strategically to install stereochemistry. In addition, upon establishment of the C-1-*exo* configuration, functional group interconversion at C-1 occurs readily even after polycycle formation, with the accomplished Curtius rearrangement as representative example of the available synthetic options. The ease by which the *exo*-1-stubstiuents of the polycycle can be manipulated suggests that if the C-1 stereochemistry is established prior to cyclization, preparation of the lolines could arise from one precursor. The late 1980s work of Yates and co-workers confirmed this hypothesis by demonstrating efficient interconversion of the lolines.[2] Tufariello and co-workers completed the first total synthesis of **1** in a concise, racemic twelve step route with <10% overall yield.

The first asymmetric total synthesis of (+)-**1** was not reported until 2000 by White and co-workers (**Scheme 1.3**).[8,34] Essential to White's route is an intramolecular acyl-

Scheme 1.3: The asymmetric total synthesis of (+)-Loline byWhite and co-workers.



nitroso Diels–Alder cycloaddition of substrate **20** (prepared in 9 steps from (*S*)-malic acid) to form pyrrolizidine skeleton. Cycloaddition only achieved a 57:43 selectivity in favor of the desired *cis* product **21** but was easily separated by column chromatography.[8] Pyrrolizidine **22** was prepared from **21** by reduction and simple functional group manipulation. With **22** available, Sharpless catalytic asymmetric aminohydroxylation installed the required *exo*-1-amine at C-1 as well as the vicinal alcohol at C-2 in modest 3:1 regioselectivity with complete preference for the convex face. It is notable that the original conditions described by sharpless and co-workers for asymmetric aminohydroxylation produced the desired regiochemistry in the highest ratio.[39] In line with Tufariello's work, White utilized the *exo*-cylic preference of the convex face of the pyrrolizidine skeleton to control the aminoalcohol construction. The synthesis closes with preparation of **24** with simple functional group interconversions from **23.** The strained ether bridge is formed under forcing conditions (180 °C in *o*-$Cl_2C_6H_4$) to afford intermediate **24** to give *N*-tosyl,kmloline **25.** Exposure of **25** to sodium naphthalenide yields (+)-**1** in 20 overall steps and negligible total yield.

White decided to form the strained bridging ether last, similar to the strategy of Tufariello, but instead chose to install the necessary hydroxy stereochemistry at C-7 instead of C-2. The implication is that the possible *in vivo* ether formation could arise from any isomeric substituent combination, but most likely through the conditions of Tufariello because of the extreme conditions required in White's synthesis. Considering that loline **1** contains only seven carbons and four contiguous stereocenters, it is unexpected that only one asymmetric synthesis is reported and is only modestly regio- and diastereoselective. The fact that loline poses a synthetic challenge is evident by only two complete syntheses existing in the literature even though its absolute structure was determined more than 40 years prior.[8,9,32-34] The work described in this thesis aimed to develop a concise route to the *lolium* alkaloids. We strived to circumvent the pitfalls discovered in the aforementioned synthetic efforts as well as apply new methodological advancements to the synthesis of the lolines. We wished to impart a unique perspective on the synthetic history of this small, topologically dense polycyclic alkaloid.[11]

At the time of writing, an asymmetric synthesis of the lolines was published by Trauner and co-workers. This synthesis is not discussed in this thesis.[40]

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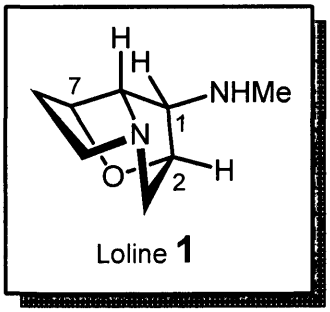
CHAPTER II

THE TOTAL SYNTHESIS OF THE LOLIUM ALKALOIDS VIA TETHERED AMINOHYDROXYLATION

Introduction and Retrosynthesis:

With the limitations of the previous syntheses in mind (Chapter I), we designed a synthetic route to the loline (**1**) (See **Table 1.1** for related lolines) that would overcome these challenges by using the tethered aminohydroxylation (TA) reaction.[1-5] Central to our strategy, the TA reaction would overcome the poor regioselectivity of the intermolecular aminohydroxylation that White and coworkers utilized in their synthesis of loline.[6,7] We initiated our synthesis from a proline derivative in order to install all required functionality on an established framework, with interception of possible biosynthetic intermediates in mind. [8,9]

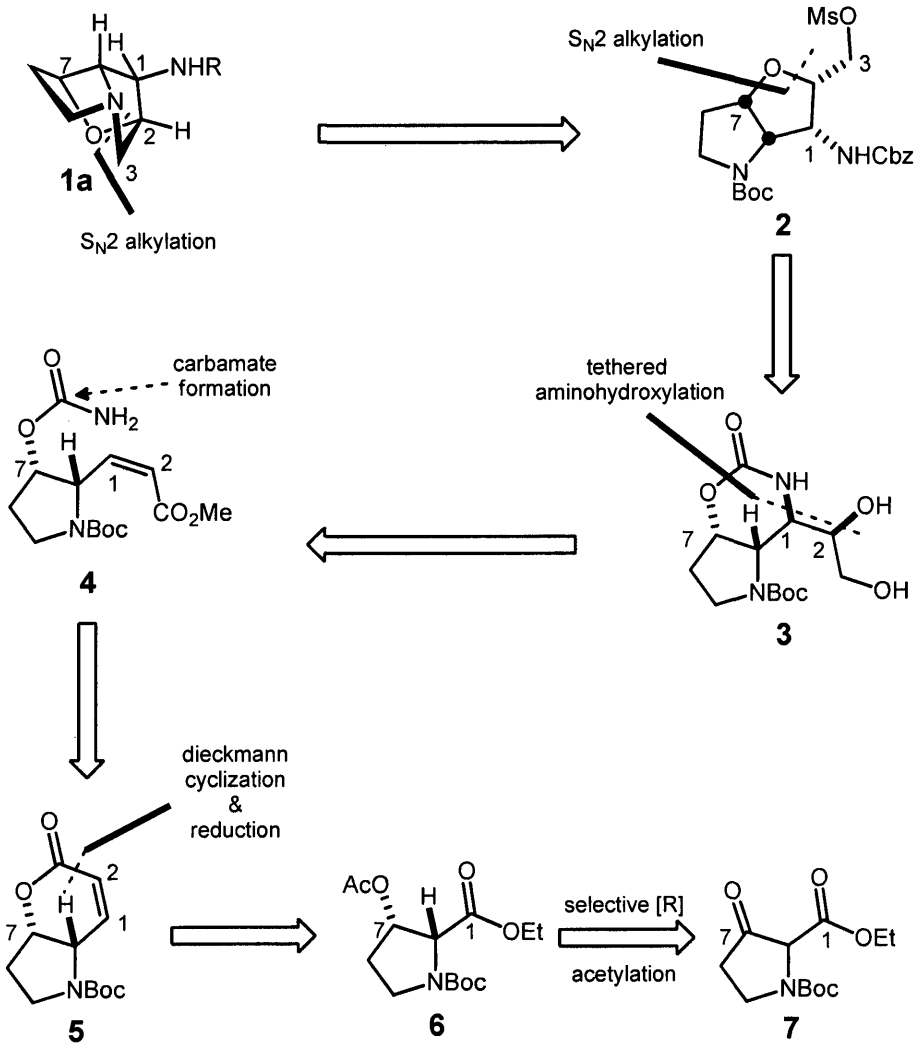
Figure 2.1: Loline



Loline **1**

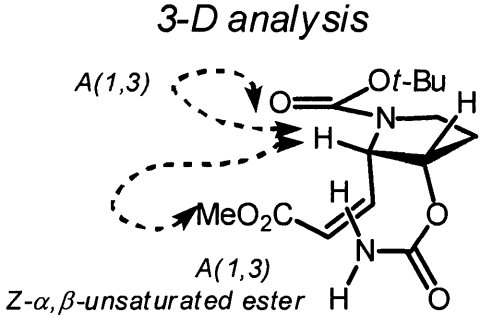
Scheme 2.1 outlines our retrosynthesis of loline core **1a**. The first pyrrolizidine disconnection between the bridgehead nitrogen and carbon 3 (C-3) suggests intermediate bicycle **2**. In the forward direction, C-N bond construction forms the second ring of the pyrrolizidine backbone. The ether bridge could arise from precursor **3** *via* alkylation between the oxygen of the C-7 hydroxy and C-2. These two disconnections complete the tricyclic core of loline. The vicinal amino alcohol moiety of **3** could be prepared by

Scheme 2.1: Retrosynthesis of first generation route.



tethered aminohydroxylation of substrate **4** because we anticipated the stereochemistry of **3** to be essential for the desired alkylations,. We hypothesized that the *A(1,3)* strain of the *Z*-olefin in substrate **4** would direct the pendant carbamate to selectively form only one diastereomer (**Figure 2.2**). Though *A(1,3)* strain is also present in the *E*-isomer of **4**, the *Z*-configuration is required to form the desired stereochemistry of **3**.[4] A brief review of the key TA reaction follows this section.

Figure 2.2: Conformational preference of TA substrate

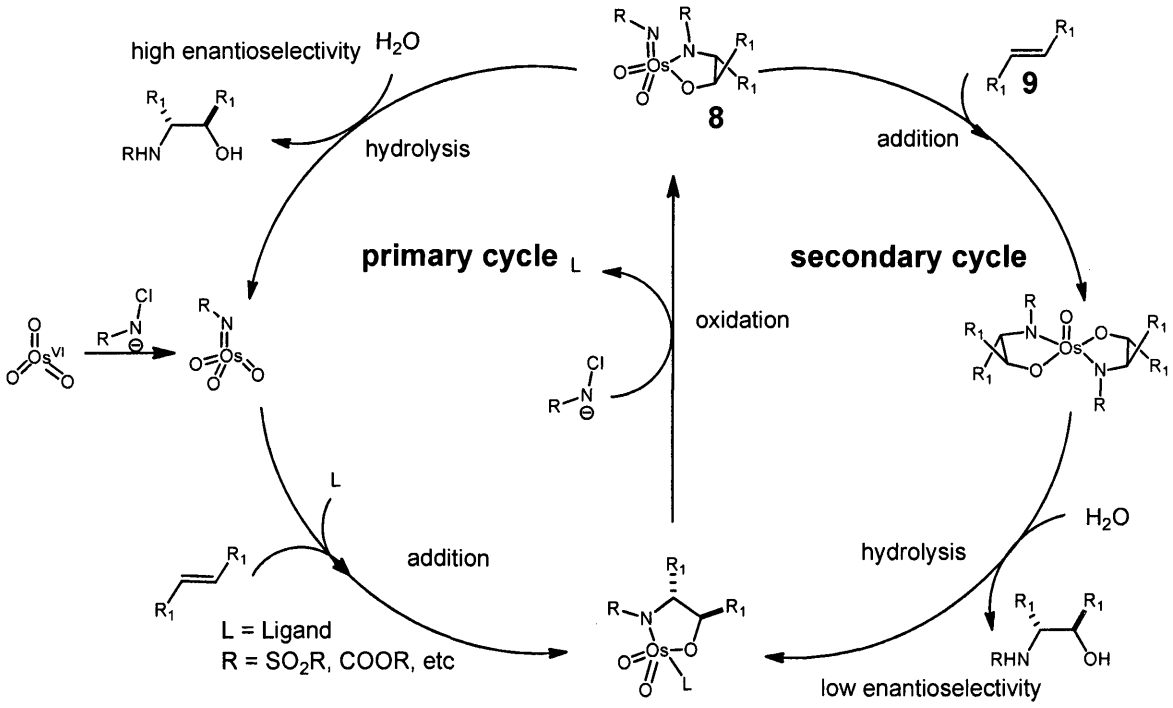


Several routes to the TA substrate **4** from **7** were pursued, but the route described subsequently proved to be the most practical. Carbamate ester **4** is traced back to unsaturated lactone **5** through acylation of the hydroxy intermediate and esterification of the resultant carboxylic acid formed by saponification. In turn, lactone **5** was thought to arise from acetylated β-hydroxy proline derivative **6** by regioselective Dieckmann cyclization to afford the desired *Z*-geometry of the resultant olefin. Reduction of the cyclic enol would give **5**. From β-ketoester **7**, we envisioned enantioselective enzymatic whole-cell yeast reduction to form the contiguous stereocenters of proline derivative **6**.[10,11]

Tethered Asymmetric Aminohydroxylation:

Sharpless and coworkers first reported the asymmetric aminohydroxlation (AA) reaction in 1996.[12] To date, AA remains a powerful tool for the stereoselective construction of vicinal amino alcohols. The reaction exposes an olefin substrate to catalytic amounts of potassium osmate reagent, $[K_2OsO_2(OH)_4]$, a stoichiometric reoxidant, and a nitrogen source. Asymmetric induction is achieved by addition of chiral ligands, usually Cinchona alkaloids.

Scheme 2.2: Asymmetric aminohydroxylation catalytic cycle[13]



It is generally thought that AA proceeds by two competitive catalytic cycles (**Scheme 2.2**).[13] The first cycle incorporates the Cinchona alkaloid ligand prior to amino alcohol installation. Ligand coordination prior to reaction with the olefin creates a facial

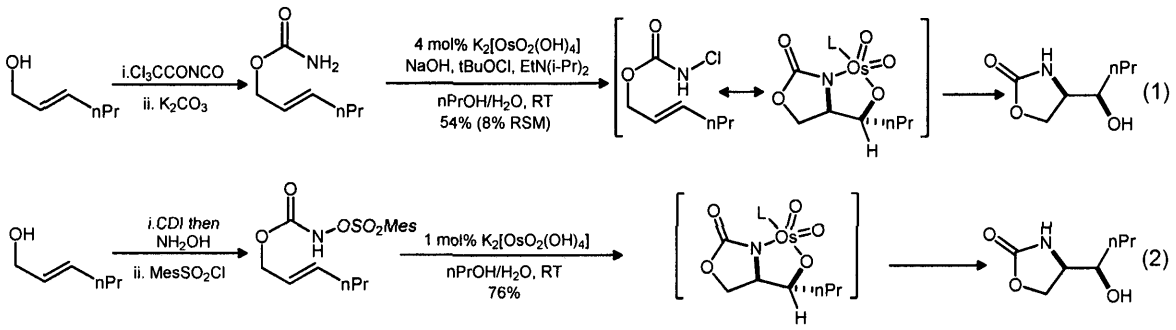
preference for reaction with the osmium species. Recent computational studies propose a possible concerted mechanism for reaction of the osmate reagent with the olefin.[14] A concerted mechanism explains the *cis* selectivity of the reaction as well as the asymmetry induced by chiral ligands. Constructive overlap of the osmium orbitals with the olefin π-bond orbitals in the transition state would require a defined geometry, thus stereoselectivity is governed by the chiral environment induced by the chincona ligands.[14]

The second catalytic cycle occurs because the product vicinal amino alcohol can compete with the amine chiral ligands for coordination with the osmium species. This is known as product inhibition. Instead of hydrolysis, the pathway circumvents recoordination of the chiral ligand to osmium because the osmium complex **8** reacts with an additional olefin **9** after reoxidation instead of coordination of the Cinchona ligands. The second catalytic cycle maintains only slight regioselectivity and is unable to induce asymmetry.[13] In addition, the reaction preference of olefins for either cycle is largely substrate dependent. In order to alleviate the uncertainty in determining the dominant pathway, an aminohydroxylation methodology with predictable selectivity needed to be developed.

Donohoe and coworkers published a communication in 2001 detailing the development of a intramolecular asymmetric aminohyroxylation that uses the substrate bound nitrogen.[4] The methodology was coined tethered aminohydroxylation (TA) because the osmium species is tethered directly to the substrate, forcing an intramolecular mechanism.[15] Donohoe reported high regioselectivity (>20:1) and *syn* diastereoselectivity, suggesting the reaction followed previously hypothesized catalytic pathways.[3,5] The first generation protocol of the TA reaction prepared an allylic

carbamate through a two step sequence from the requisite allylic alcohol (**Scheme 2.3**).[4] The first procedure (**Eq 1**) with *tert*-butylhypochlorite was limited by low yields because of competitive chlorination of the olefin. In addition, this side reaction completely prevents the construction of six-membered 1,3-oxazinan-2-ones (cyclic carbamates) from homoallylic alcohols (Example not shown).[13]

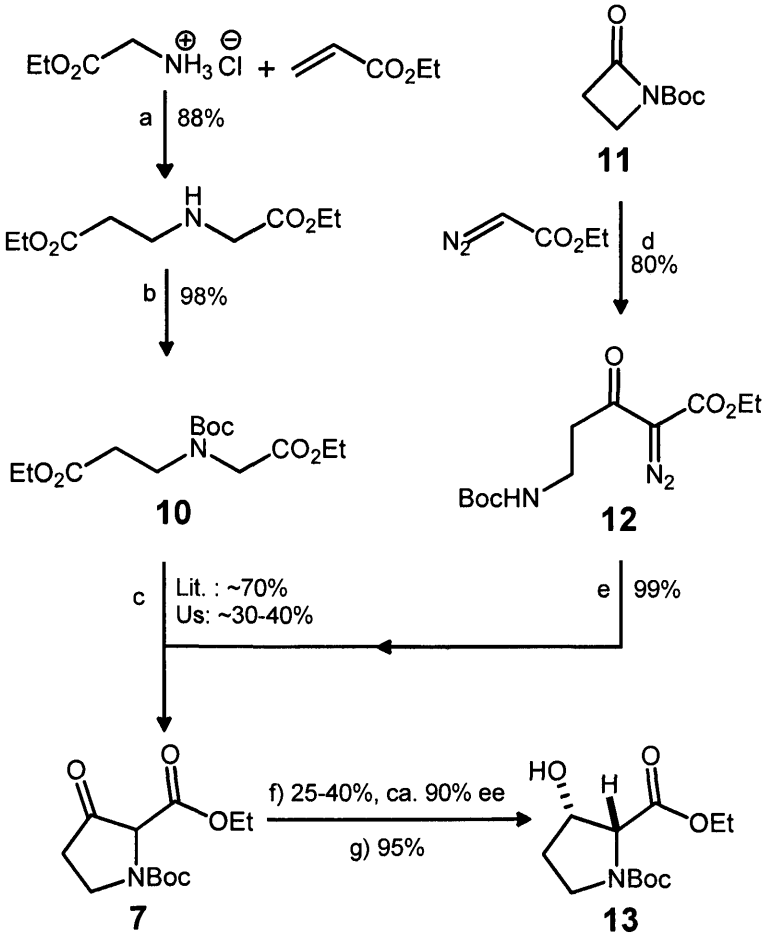
Scheme 2.3: First and second generation TA reaction protocol[1,13,15]



To overcome this limitation, Donohoe and coworkers built on the work of Taylor and coworkers which used homoallylic sulfonamates to promote TA reactivity.[16] Donohoe's group sought to replace the *in situ* *N*-chloro-carbmates with *N*-sulfonyloxy or *N*-carbonyloxy derivatives (**Eq 2**).[1,2] The modification was compatible with homoallylic alcohol substrates and dramatically improved overall yields.[1,2]

With the synthetic strategy to **1** planned, we first turned our attention to preparation of β-hydroxy proline derivative **13** (**Scheme 2.4**). We envisioned that **13** could be prepared by reduction of the *cis*-3-oxo proline **7**. Rapoport and coworkers have previously reported a synthesis of **7.** Their route is initiated by hetereo-conjugate addition of ethyl glycinate with ethyl acrylate, followed by Boc protection of the free amine to afford intermediate **10**. Dieckmann cyclization of **10** to afford **7** concludes this route.[10]

Scheme 2.4: Synthesis of *cis*-3-hydroxyproline derivative



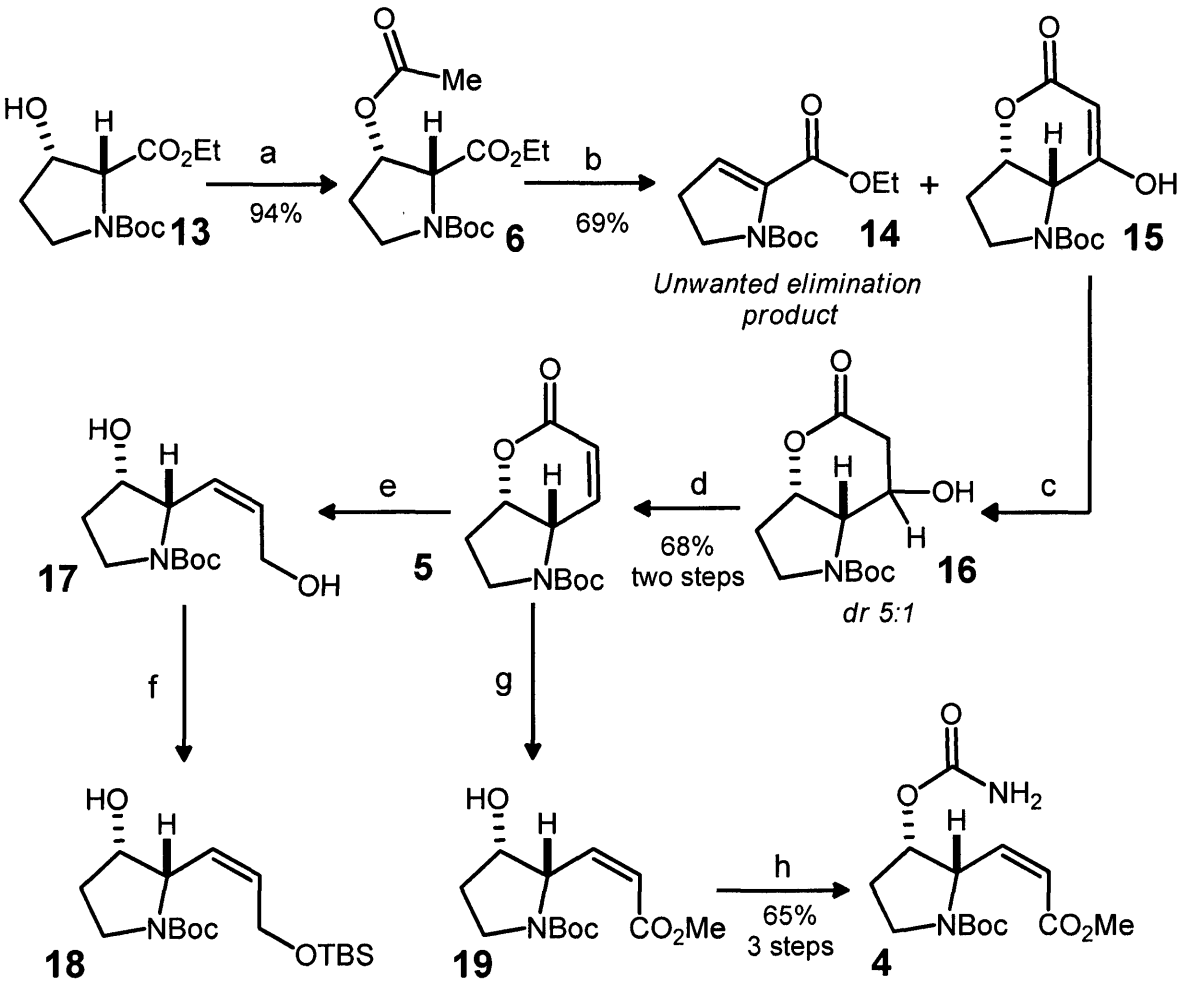
a) Et_3N, EtOH 0 °C; b) Boc_2O, DCM/NaOH rt; c) LiHMDS,THF -78 °C; d) LiHMDS, THF, -78 °C; e) $Rh_2(OAc)_4$, tol 90 °C; f) Baker's yeast; g) $NaBH_4$, MeOH.

Williams and coworkers improved the regioselectivity of Rapoport's method by using LiHMDS in anhydrous THF at –78 °C is to give the desired regeoisomer **7** in ~70% (us 30-40%) yield. [17] We postulate that the kinetic enolate forms preferably giving only the desired cyclization regioisomer **7**.

In an attempt to streamline our synthesis of **7** because our preparation afforded low overall yields (25%–45%), we also developed a more concise method to multi-gram quantities. Our route commences with *N*-Boc-2-azetidinone **11** (commercially available or prepared in one step)[18] exposed to lithiated ethyl diazoacetate to form substrate **12** through a Claisen condensation. Subsequent exposure to a rhodium catalyst converts **12** to **7** *via* N-H carbene insertion in quantitative yield.[19,20] This alternative synthesis of **10** is achieved in 80% reproducible overall yield, with chromatography not required in the final step.

From **7** we proposed the preparation of enantiopure **13** by whole-cell bioreduction with Baker's yeast in non-fermenting conditions. Preparation of **9** by Baker's yeast reduction under previously reported by the research groups of Knight and Gellman.[21,22] Unfortunately, in our hands, we could not reproduce the 80% yield reported by Knight and Gelllman. For economy and expedience we chose to prepare the racemic *cis*-3-hydroxyproline ester **13** *via* sodium borohydride reduction.[17] The diasteroselectivity of sodium borohydride reductions are well understood and have been exploited previously in cyclic systems to create *cis* stereochemistry (dr > 10:1).

Scheme 2.5: Synthetic route to TA substrate

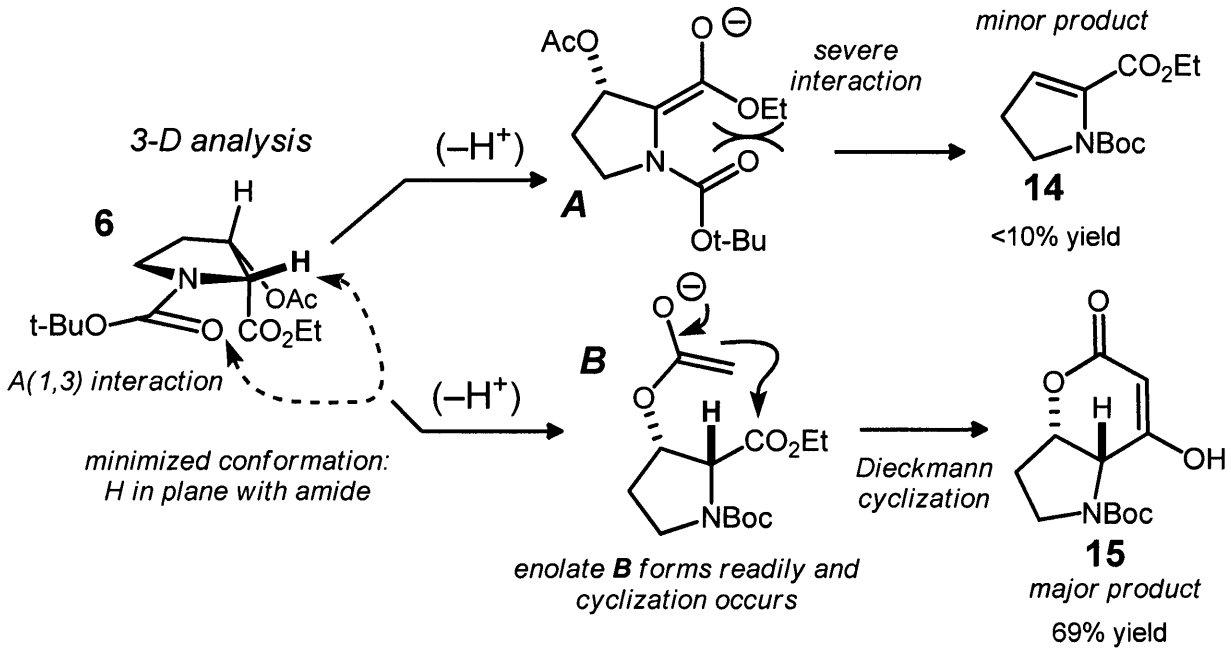


a) Ac_2O, NEt_3,DMAP, DCM; b) LiHMDS, -78 C THF; c) *t*-$BuNH_2$•BH MeOH, 0 °C; d) i. Ac_2O, NEt_3,DMAP, DCM ii. DBU; e) DIBAL-H, DCM -78 C; f) TBS-Cl, imid. DMF; g) i. LiOH, THF/H_2O ii. MeI, K_2CO_3; h) i. $Cl_3CCONCO$ ii. MeOH, $NaHCO_3$.

With *cis*-3-hydroxyproline **13** prepared, the next phase in our synthesis was to construct the TA substrate. We anticipated that Dieckmann cyclization of acetylated derivative **6** (**Scheme 2.5**) would produce the required *Z*-olefin geometry. Conformational analysis (**Figure 2.3**) of **6** predicts that the acetate moiety is in the vicinity of the *cis*-ester because of minimized allylic *A(1,3)* strain. Slow addition of LiHMDS down the side of a reaction vessel containing **6** at –78 °C provided the desired

product **15** in the highest yield (69%). We found that LiHMDS needed to be as close to –78 °C as possible before coming into contact with substrate **6** in order to minimize the formation of undesired elimination product **14**. The enol tautomer **15** predominates at room temperature as determined by NMR spectroscopy (>20:1). Undesired **14** can be removed my acid/base extraction workup.

Figure 2.3: Conformational analysis of Dieckmann cyclization substrate

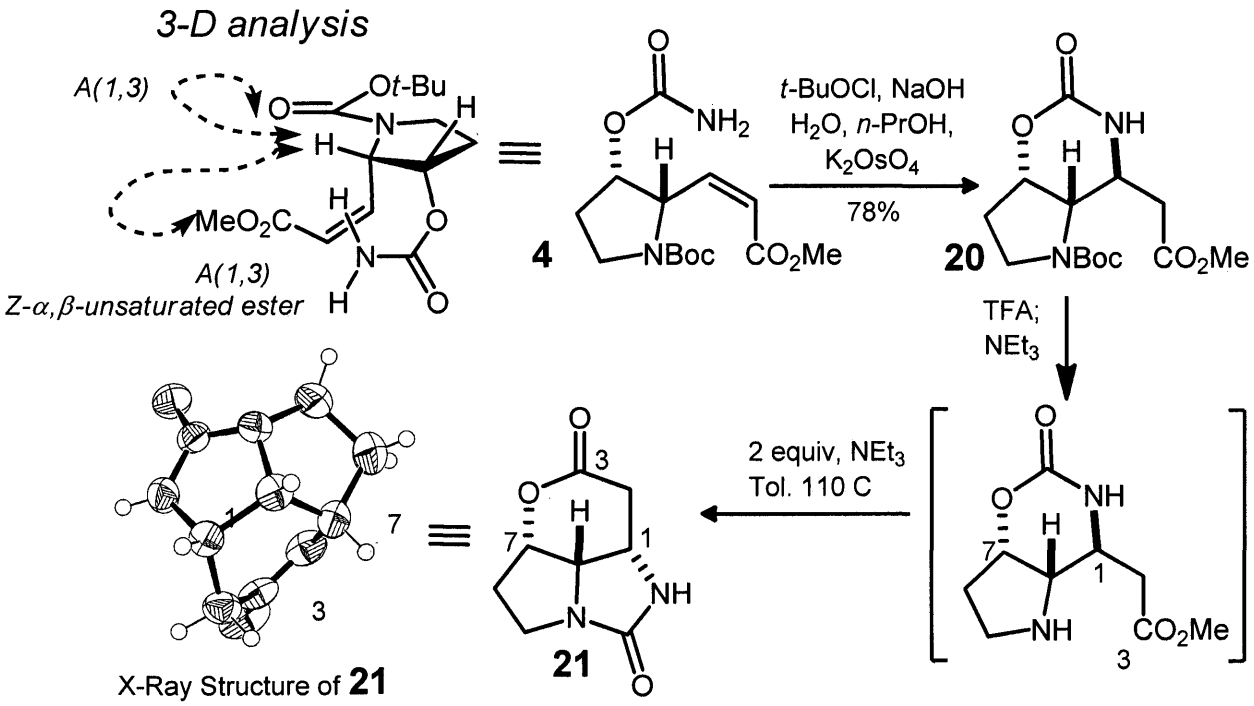


To affect the reduction of enol **15** we explored multiple conditions. Palladium hydrogen insertion into the derived triflate of enol **15** was anticipated to produce the desired α,β-unsaturated lactone **5** but did not prove viable. Alternatively, reduction by borane complexed with *tert*-butylamine in methanol solution buffered with citric acid gave the desired β-hydroxy lactone **16** in a 5:1 diastereomeric mixture as determined by NMR spectroscopy. Acetylation and base mediated elimination of **16** afforded α,β-unsaturated lactone **5**. DBU (0.3 equivalents) was added to the reaction flask in order to

drive the elimination to completion. This sequence afforded **5** in a 68% three-step yield with purification not necessary.

With *Z*-olefin **5** in hand, our attention turned to establishing the pendant carbamate of TA substrate **4**. Originally, we hypothesized that reduction to prepare diol **17** and selective protection could eventually produce substrate **4** (**Scheme 2.5**). The selective protection of the primary allylic alcohol as the TBS ether produced a complex mixture of regeoisomers even though literature precedent existed for the desired regioselectivity.[23] Instead, we developed a saponification/esterification sequence to prepare **19**. Addition of $LiOH/H_2O$ saponified lactone **5**. Subsequent addition of K_2CO_3 and alkylation with MeI formed the methyl ester **19**. Synthesis of carbamate **4** from

Figure 2.4: Hetereoconjugate addition of methyl ester substrate



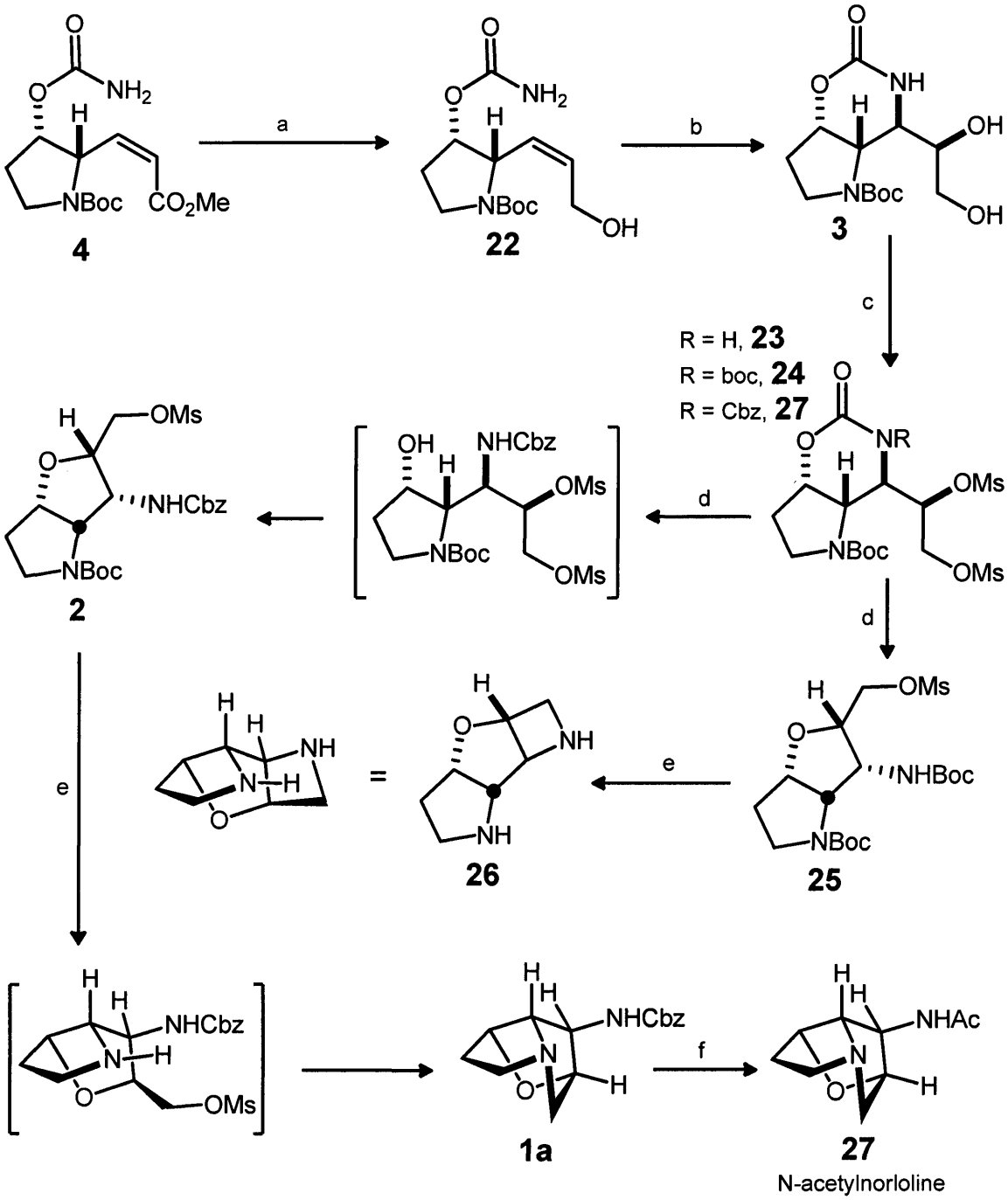
alcohol **19** was accomplished with trichloroacetylisocyanate to afford **4** in a respectable 65% three step yield.

With substrate **4** constructed, we anticipated that TA would occur readily between the carbamate and the pendant olefin moiety. We postulated that the *A*(1.3) strain of the *Z*-olefin would dictate the diasteroeslectivity because of conformational stability (**Figure 2.4**). When exposed to first generation TA conditions (use of tBuOCl as the oxidant), hetereoconjugate addition predominates to form bicycle **20.** Though conjugate addition was not desired, the 1,3-oxazinan-2-one (cyclic carbmate) was formed in high diastereoselectivity (>20:1), confirming our conformational predictions. Subsequent exposure of **20** to 25% TFA in DCM cleaved the Boc protecting group.

When exposed to triethylamine cyclization between the amine and the pendant methyl ester was not observed. Under forcing conditions (refluxing toluene), condensation of the amine at the cyclic carbamate occurred followed by lactonization to form the undesired tricyclic urea **21**. The absolute structure of **21** was confirmed by X-ray crystallography. The inability of the substrate **20** to undergo constructive amide formation to form the pyrrolizidine requires cleavage of the cyclic carbamate prior to alkylation in subsequent attempts.

We hypothesized that reduction of the methyl ester **4** to the allylic alcohol **22** would prevent hetereoconjugate addition while maintaining reactivity (**Scheme 2.6**). Reduction of **4** with three equivalents of DIBAL-H afforded **22** in 73% yield. Exposing **22** to first generation TA reaction conditions produced **3** as a single diastereomer in a

Scheme 2.6: Tethered aminohydroxylation to loline core and N-acteylnorloline.



a) DIBAL-H, DCM, -78 °C; b) K_2OsO_4, *n*-PrOH, NaOH, *i*-Pr_2NEt;
c) i. MsCl, Pyr ii. Boc_2O, DMAP, DCM iii. Cbz-Cl, DMAP, THF
d) C;s_2CO_3, MeOH; e) i. TFA 25%, DCM ii. Et_3N; f) H_2, Pd/C ii. Ac_2O

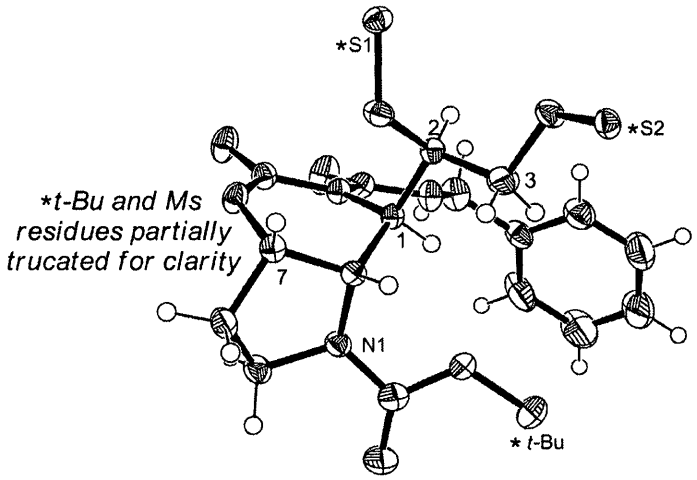
respectable 68% yield with ~15% recovered starting material. The formation of the six membered cyclic carbamate is noteworthy because in initial communications, Donohoe and coworkers found that TA of homoallylic carbamates were not viable substrates because of competing side reactions.[1,15]

With the four contiguous stereocenters of loline skeleton successfully installed, we turned our efforts toward forming the pyrrolizidine skeleton and the strained ether bridge. Formation of bis-mesylate **23** was accomplished by exposing **3** to methanesulfonyl chloride in pyridine. Our previous exploration into condensation of the Boc-protected amine **20** with the methyl ester established the need to cleave the cyclic carbamate prior to formation of the pyrrolizidine skeleton (**Scheme 2.4**). From the work of Rojas and coworkers, we determined that the *tert*-butoxycarbonyl (Boc) protected imide **24** would allow regioselective cleavage of the endocyclic carbamate moiety.[24] Imide **24** was prepared with $(Boc)_2O$ followed methanolysis of **24** with cesium carbonate afforded the endocyclic cleavage product **25.**

Upon cleavage of the cyclic carbamate, we observed the concomitant alkylation of the exposed hydroxy in **24** by the C-2 mesylate to afford the desired ether bond of bicycle **25**. Unfortunately, Boc cleavage of **25** produces competitive alkylation of the pendant amine resulting in tricycle **26** instead of the desired alkylated secondary amine product. Though the formation of four-membered hetereocycles is retarded relative to the formation of their five-membered counterparts, in the case of substrate **25**, the proximity of the pendant amine to the mesylate dictated reactivity.

In light of these results, differential protection of the amide nitrogens was required to insure proper amine alkylation. The benzyloxycarbonyl (Cbz) protecting group was chosen because it can be cleaved preferentially to the Boc protecting group. Synthesis of **27** proved more difficult than **24**, but once proper conditions were found (triethylamine, DMAP, and benzyloxycarbonyl chloride) it was prepared in 94% two step yield. X-ray crystallographic analysis of **27** confirmed our structural assignment and verified the diastereoselectivity of the tethered aminohydroxylation (**Figure 2.5**).

Figure 2.5: X-ray structure of **31**.



31

Multiple cleavage conditions were considered for substrate **27.** Rojas and co-workers had originally reported sodium methoxide in toluene as the most effective method to cleave the endocyclic carbamate moiety of Cbz protected cyclic imides.[24] In our hands, the cesium carbonate conditions used for the previous substrate **24** proved most effective. Due to poor regioselectivity, the desired heterobicycle **2** was isolated in only 35% yield. The major product was the undesired exocyclic cleavage byproduct **23**

(45% yield) which was easily recycled to **27**. Removal of the Boc group is followed by exposure to triethylamine afforded the *exo*-1-aminopyrrolizidine-2,7-ether skeleton **1a** of the lolium alkaloids in quantitative yield. The high yielding synthesis of **1a** is a testament to the reactivity of the secondary amine with the pendant mesylate.

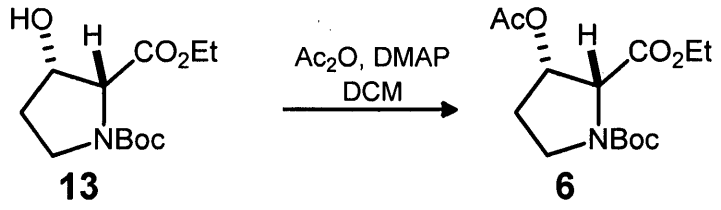
With the loline skeleton in hand, *N*-acetylnorloline (**Table 1.1**) was synthesized as a prototypical family member of the alkaloids. The Cbz group was cleaved by hydrogenation. Then the *exo*-primary amine was acetylated with acetic anhydride to afford *N*-acetylnorloline in 71% yield over two steps. The ^{1}H and ^{13}C NMR spectra of synthetic acetylnorloline are identical to the natural isolated material.[25] Interconversion between lolines was previously reported by Petroski and coworkers, therefore facile synthesis of the loline skeleton provides access to related family members. [25]

Conclusion:

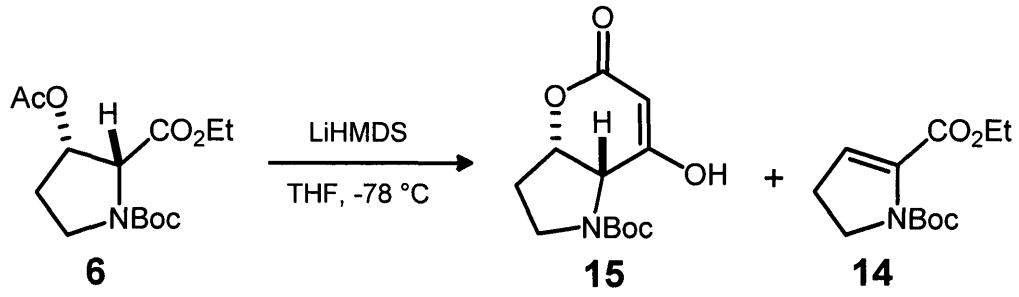
In conclusion, we have developed a synthesis to loline alkaloids. Central to our route is the distereoselective TA reaction. The high selectivity and yield of the TA to form a six membered cyclic carbamate is noteworthy because homoallylic carbamate TA substrates traditionally do not react productively. Our success is evidence of substrate conformation controlled by *A(1,3)* strain which dictates the predictable diastereoselectivity of the TA reaction. Synthesis of our TA substrate is labor intensive and late stage steps in our route suffer limited regioselectivity that at present prevents the gram-scale preparation of lolines. Even though our synthesis was diastereoselective, we were unable to prepare the lolines asymmetrically. In order to address these limitations, studies into the expedient synthesis of TA substrate **4** from chiral pool starting material have been initiated. The investigations aimed to improve our first synthetic mission are reported in the following Chapter (III) of this thesis.

Experimental Section

General Information: All reactions were carried out under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring unless otherwise indicated. Acetonitrile, THF, toluene, and Et_2O were degassed with argon and purified by passage through a column of molecular sieves and a bed of activated alumina.[26] Dichloromethane was distilled from CaH_2 prior to use. All reagents were used as received unless otherwise noted. Flash column chromatography[27] was performed using SiliCycle siliaflash P60 silica gel (230–400 mesh). Analytical thin layer chromatography was perfomed on SiliCycle 60Å glass plates. Visualization was accomplished with UV light, anisaldehyde, ceric ammonium molybdate, potassium permanganate, or ninhydrin followed by heating. Film infrared spectra were recorded using a Digilab FTS 7000 FTIR spectrophotometer. Single crystal determinations were carried out using a Bruker *SMART Apex II* diffractometer using graphite-monochromated Cu K radiation. ^1H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) spectrometer are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm) or tetramethylsilane (0.00 ppm). The NMR spectra of all compounds containing *t*-butoxyl carbonyl (Boc) residues are complicated by carbamate rotamers. Proton-decoupled ^{13}C-NMR spectra were recorded on a Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.00 ppm). All compounds were judged to be homogeneous (>95% purity) by ^1H and ^{13}C NMR spectroscopy. Mass spectra data analysis was obtained through positive electrospray ionization (w/ NaCl) on a Bruker 12 Tesla APEX–Qe FTICR-MS with an Apollo II ion source.

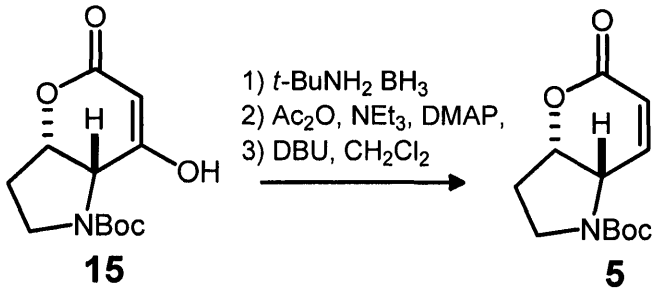


Synthesis of (±)-*N*-Boc-*cis*-3-acetoxyproline ethyl ester (6). To (±)-*N*-Boc-*cis*-3-hydroxyproline ethyl ester[17] **13** (2.00 g, 7.7 mmol) in CH_2Cl_2 (25 mL) was added NEt_3 (3.2 mL, 23 mmol), Ac_2O (2.3 mL, 23 mmol), and DMAP (0.095 g, 0.77 mmol). The reaction mixture was stirred under nitrogen for 16 h at 23 °C, diluted with 1M HCl (100 mL), and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography on silica gel (elution: 60% EtOAc in hexane) to afford the desired product **6** (2.09 g, 94% yield) as a clear oil. The ^1H NMR spectum of **6** was complicated by carbamate rotamers: TLC (60% EtOAc in hexane), R*f*: 0.45 ($KMnO_4$); IR (film) 3854, 3745, 2983, 2939, 2905, 1756, 1718, 1408, 1239, 1171, 1144, 1104, 1057, 1031, 919, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46–5.42 (m, 1H, C_3H), 4.56 and 4.50 (d, J = 7.0 Hz, 1H, C_2H), 4.25–4.14 (m, 2H, OEt), 3.69–3.46 (m, 2H, C_5H_2), 2.13–1.08 (m, 2H, C_4H_2), 2.03 (s, 3H, Ac), 1.46–1.41 (s, 9H, *t*-Bu), 1.36–1.25 (m, 3H, OEt); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.3, 153.6, 80.3, 72.9, 61.2, 61.0, 44.0, 29.9, 28.2, 20.7, 14.3; Exact mass calcd for $C_{14}H_{23}NO_6Na^+$ $[M+Na]^+$, 324.1418. Found 324.1420.



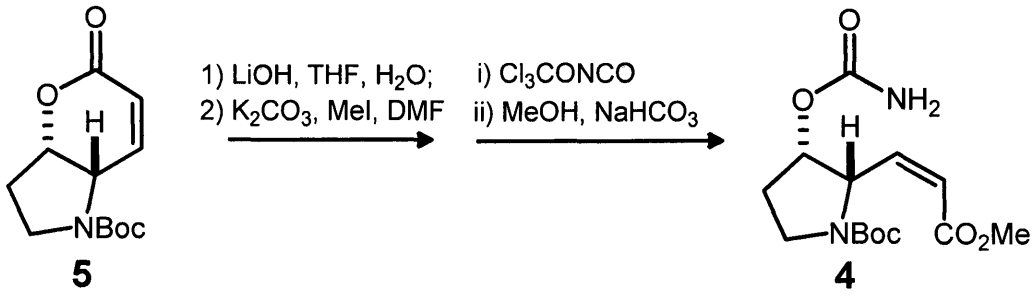
6 15 14

Preparation of (±)-Enol lactone (15). To a solution of compound **6** (1.34 g, 4.45 mmol) in THF (10.0 mL) at –78 °C was added a cold solution (–78 °C) of LiHMDS (1.0M soln in THF, 8.6 mmol, 1.95 equiv) in THF (20 mL) *via* cannula over 20 min. After stirring 1 h at –78 °C, the reaction was slowly warmed to –20 °C over 2 h and then quenched with water (100 mL). The resulting mixture was partitioned between Et_2O/hexanes (1:1, 150 mL total) and 1M NaOH (100 mL). The aqueous layer was removed and the organic layer was extracted with additional 1M NaOH (2 x 50 mL). The combined aqueous layers were acidified with conc. HCl (18 mL) to pH 4 and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on silica gel (elution: 30→80% EtOAc in hexanes) to afford **15** (0.78 g, 69% yield) as a colorless solid: mp 69–71 °C; TLC (40% EtOAc in hexanes), R*f*: 0.55 (UV, CAM); IR (film) 3451, 2982, 1687, 1626, 1422, 1369, 1250, 1221, 1162, 949, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.42 (br s, 1H, ROH), 5.31 (s, 1H, C_2H), 5.09–5.05 (ddd, J_1 = 9.8 Hz, J_2 = 5.1 Hz, J_3 = 3.39 Hz, 1H, C_7H), 4.41 (d, J = 6.2 Hz, 1H, C_1H), 3.71 (m, 1H, $C_{5a}H$), 3.50 (m, 1H, $C_{5b}H$), 2.32–2.17 (m, 2H, C_6H), 1.51 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.4, 158.6, 93.4, 83.4, 76.9, 54.5,



Synthesis of α,β-Unsaturated lactone (5). To a solution of compound **15** (10.70 g, 42.0 mmol) in MeOH (420 mL) at 0 °C was added *t*-$BuNH_2$•BH_3 complex (5.850 g, 67.2 mmol, 1.6 equiv) in one portion followed by addition citric acid (9.03 g, 47.0 mmol, 1.12 equiv) as a 1M solution. After stirring 1.5 h at 0 °C, the solvent was evaporated *in vacuo*. The residue was partitioned between 0.5M HCl (1 L) and EtOAc (300 mL). The organic layer was removed and the aqueous layer extracted with additional EtOAc (3x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (300 mL), brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil (8.01 g) was dissolved in CH_2Cl_2 (150 mL) and cooled to 0 °C. To this solution was added DMAP (0.386 g, 3.14 mmol, 0.1 equiv), NEt_3 (13.1 mL, 94.0 mmol, 3.0 equiv), and Ac_2O (6.43 mL, 63.0 mmol, 2.0 equiv). The reaction mixture was allowed to warm to 23 °C overnight and partitioned between 1M HCl (200 mL) and CH_2Cl_2 (150 mL). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4 x 150 mL). The combined organic layers were washed with saturated $NaHCO_3$ (200 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was dissolved in CH_2Cl_2 (60 mL) and DBU (3.0 mL, 20 mmol, 0.66 equiv) was added. The reaction mixture was stirred for 2 h at 23 °C, after which time the solution was partitioned between 1M HCl (200 mL) and CH_2Cl_2 (200 mL). The organic layer was removed and the aqueous layer was

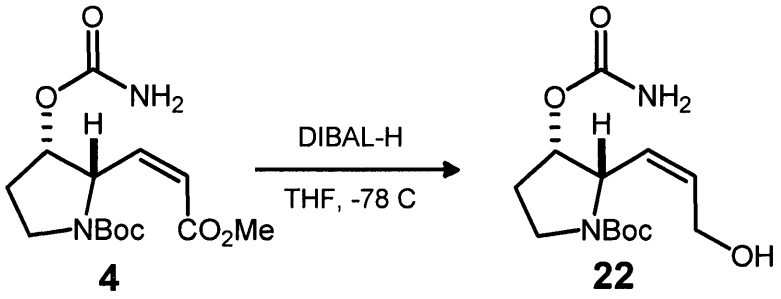
extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting light yellow solid was purified by flash chromatography on silica gel (elution: 35→100% EtOAc in hexanes) to afford **5** (6.830 g, 68% yield over the 3 steps) as a colorless solid: mp 98-99 °C; TLC (60% EtOAc in hexanes), R*f*: 0.40 (UV, $KMnO_4$); IR (film) 2980, 2937, 1730, 1695, 1401, 1368, 1248, 1171, 1101, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17, 6.93 (m, J_1 = 9.8 Hz, J_2 = 4.4 Hz, 1H, C_1H), 6.03 (m, J = 9.8 Hz, 1H, C_2H), 5.05 (m, 1H, C_8H), 4.25 (m, 1H, C_7H), 3.65–3.47 (m, J_1 = 2.0 Hz, J_2 = 8.6, Hz J_3 = 7.0 Hz, 2H, C_5H), 2.22 (m, 2H, C_6H), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.6, 154.1, 153.5, 143.0, 142.9, 120.7, 120.4, 80.7, 80.4, 79.7, 79.5, 51.2, 51.0, 44.6, 44.1, 31.4, 30.8, 28.3; HRMS (ES+): Exact mass calcd for $C_{12}H_{17}NO_4Na^+$ $[M+Na]^+$, 262.1050. Found 262.1037.



5 **4**

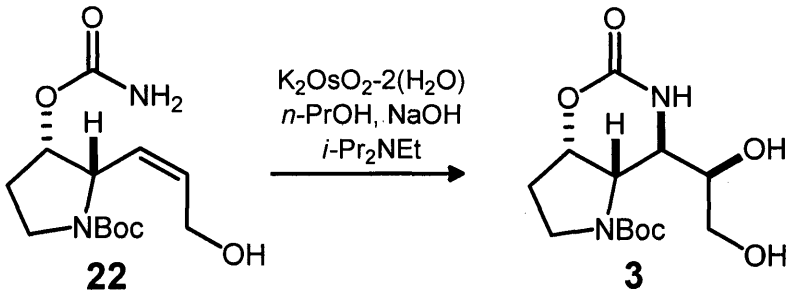
Synthesis of α,β-Unsaturated methyl ester (4). To a solution of compound **5** (6.83 g, 28.6 mmol) in THF (135 mL) and H_2O (45 mL) was added $LiOH•H_2O$ (1.44 g, 34.3 mmol, 1.2 equiv) at 23 °C. After stirring 5 h, the reaction mixture was partitioned between 0.1M HCl (300 mL) and EtOAc (100 mL). The organic layer was removed and the aqueous layer was extracted with additional EtOAc (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was dissolved in DMF (95 mL) at 23 °C and K_2CO_3 (4.39 g, 34.3 mmol, 1.2 equiv) and MeI (8.9 mL, 143 mmol, 5.0 equiv) were added. After stirring for 2 h, the reaction mixture was diluted with saturated $NaHCO_3$ (100 mL) and H_2O (100 mL) and extracted with EtOAc (200 mL). The organic layer was removed and the aqueous layer extracted with additional EtOAc (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was dissolved in CH_2Cl_2 (150 mL) and cooled to 0 °C. After addition of trichloroacetyl isocyanate (3.50 mL, 29.8 mmol, 1.05 equiv) the solution was stirred for 10 min and concentrated *in vacuo*. The residue was dissolved in MeOH (100 mL) and cooled to 0 °C. To this solution was added solid $NaHCO_3$ (2.0 g, 23.8 mmol) and the reaction vessel allowed to warm to ambient temperature overnight. The reaction mixture was diluted with brine (150 mL) and H_2O (150mL) and extracted

with EtOAc (4 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography on silica gel (elution: 60→100% EtOAc in hexanes) to afford **4** (5.820 g, 18.5 mmol, 65% yield over the 3 steps) as a colorless oil: TLC (60% EtOAc in hexanes), R*f*: 0.60 (UV, $KMnO_4$); IR (film) (3451, 3362, 3204, 2978, 2251, 1722, 1393, 1173, 1048) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.16–6.08 (m, 1H, C_1H), 5.86 (m, 1H, C_2H), 5.50 (m, 1H, C_7H), 5.45 (m, 1H, C_8H), 4.84 (br. s, 2H, NH), 3.69 (s, 3H, MeO), 3.64 (m, 1H, $C_{5b}H$), 3.51–3.44 (dt, J_1 = 10.1 Hz, J_2 = 6.6 Hz, 1H, $C_{5a}H$), 2.13–1.96 (m, 2H, C_6H), 1.43–1.36 (m, 9H, *t*-bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 155.7, 147.4, 119.7, 80.0, 77.2, 76.5, 58.4, 51.3, 44.4, 30.7, 28.2; HRMS (ES+): Exact mass calcd for $C_{14}H_{22}N_2O_6Na^+$ $[M+Na]^+$, 337.1370 Found 337.1370.



4 22

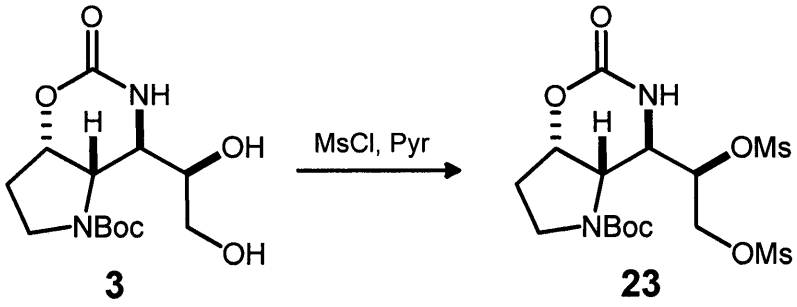
Synthesis of Allylic alcohol (22). To a solution of compound **4** (0.464 g, 1.50 mmol) in CH_2Cl_2 (12.0 mL) was added a freshly-prepared 1M solution of dibal-H (4.5 mL, 4.5 mmol, 3.0 equiv) dropwise at –78 °C. After stirring 1.5 h at –78 °C, the reaction was quenched with MeOH (2 mL). A saturated solution of sodium potassium tartrate (Rochelle's salt, 15 mL) was added and the reaction mixture was stirred vigorously overnight. The resulting clear biphasic solution was transferred to a separatory funnel and the organic layer was removed. The aqueous layer was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and condensed *in vacuo*. The resulting light yellow oil was purified by flash chromatography on silica gel (elution: 85→100% EtOAc in hexanes) to afford **22** (0.315 g, 73% yield) as a colorless oil. A small amount of unreacted starting material **4** (0.062 g 13%) was recovered: TLC (1% MeOH in EtOAc), R*f*: 0.10 ($KMnO_4$); IR (film) 3431, 3352, 3204, 2980, 1714, 1675, 1333, 1169, 949, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H, C_2H), 5.34 (s, 2H, NH_2), 5.19 (m, 1H, C_8H), 5.12–5.07 (dd, J_1 = 6.6 Hz, J_2 = 7.0 Hz, 1H, C_1H), 4.93 (m, 1H, C_7H), 4.30–3.94 (m, 2H, C_3H), 3.48 (m, 2H, C_5H), 2.18–1.98 (m, 2H, C_6H), 1.39 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 132.2, 127.2, 80.1, 73.8, 57.1, 55.2, 43.8, 30.8, 29.3, 28.3; HRMS (ES+): Exact mass calcd for $C_{13}H_{22}N_2O_5Na^+$ $[M+Na]^+$, 309.1421. Found 309.1416.



Synthesis of Diol (3). To a solution of compound **22** (1.47 g, 5.14 mmol) in *n*-propanol (64.0 mL) was added a freshly-prepared solution of NaOH (0.08M, 58.0 mL, 4.63 mmol, 0.9 equiv). After stirring for 5 min, *t*-butyl hypochlorite[1,28] was added (0.560 mL, 5.14 mmol, 1.0 equiv). After stirring an additional 5 min, *i*-Pr_2NEt was added (0.087 mL, 0.514 mmol, 0.1 equiv) followed by potassium osmate dihydrate ($K_2OsO_4 \cdot 2H_2O$, 0.025 g, 0.07 mmol, 0.01 equiv). The reaction mixture was stirred for 20 h with the hood lights off. The reaction mixture was quenched with sodium sulfite (0.50 g) and stirred 30 min before diluting with brine (200 mL) and extracting with EtOAc (5x 200 mL). The organic portions were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography on silica gel (elution: 0→8% MeOH in $CHCl_3$) to afford **3** (1.075 g 68% yield) as a colorless solid. A small amount of unreacted starting material **22** (0.260g 17%) was also recovered: mp 194 °C; TLC (10% MeOH in $CHCl_3$), R*f*: 0.25 (CAM); IR (film) 2977, 2933, 2896, 2358, 2331, 1696, 1650, 1368, 1291, 1167, 1112, 1039, 894 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 5.14 (m, 1H, C_8H), 4.20 (m, 1H, C_2H), 4.10–3.94 (m, 1H C_1H), 3.73 (m, 1H, C_7H), 3.70 (m, 1H, $C_{3a}H$), 3.69–3.66 (m, 1H, $C_{3b}H$), 3.61–3.59 (m, J = 5.47 Hz, 1H, $C_{5b}H$), 3.31–3.28 (m, 1H, $C_{5a}H$), 2.08–2.06 (m, 2H, C_6H), 1.47 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, CD_3OD)

[1] *t*-Butyl hypochlorite was prepared by the established procedure. It was stored in amber glass bottles at –10 °C and used within 4 weeks of preparation. Mintz, M. J.; Walling, C. *Org. Synth.* **1973**, *Col. Vol 5*, 184; **1969**, *Vol. 49*, 9.

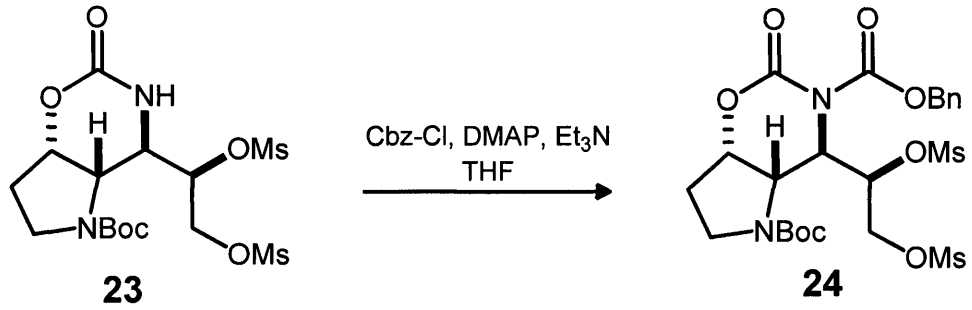
δ 154.9, 154.4, 80.9, 80.4, 80.0, 73.6, 63.2, 54.1, 53.7, 52.1, 45.2, 31.8, 27.5; HRMS (ES+): Exact mass calcd for $C_{13}H_{22}N_2O_6Na^+$ $[M+Na]^+$, 325.1370. Found 325.1370.



3 **23**

Synthesis of Bis-mesylate (23). To a solution of diol **3** (0.123 g, 0.40 mmol) in pyridine (4.0 mL) was added MsCl (0.093 mL, 1.2 mmol, 3.0 equiv). The reaction mixture was stirred overnight at 23 °C and concentrated *in vacuo* to remove the bulk of excess pyridine and diluted with CH_2Cl_2 (10 mL). The solution was washed with a 1:1 mixture of brine and H_2O (10 mL). The organic portion was removed and the aqueous portion was extracted with additional CH_2Cl_2 (2 x 10 mL). The combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow product was purified by flash chromatography on silica gel (elution: 60→100% EtOAc in hexanes) to afford bis-mesylate **23** (0.180 g, 98% yield) as a light yellow solid: mp 88–91 °C; TLC (5% MeOH in EtOAc), R*f*: 0.50 (ninhydrin); IR (film) 3012, 2978, 2937, 2362, 1700.2, 1395, 1363, 1174.7, 1117, 918, 756cm^{-1}; NMR spectrum of **23** was complicated by carbamate rotamers.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–6.90 (m, 1H, NH_1R), 5.02, 5.21 (m, 1H, C_2H), 4.89, 5.11 (m, 1H, C_8H), 4.62 (m, 1H, C_7H), 4.54 (m, J = 4.3 Hz, 1H, C_1H), 4.14–3.90 (m, 2H, C_3H), 3.83–3.67 (m, 1H, $C_{5b}H$), 3.40 (m, 1H, $C_{5a}H$), 3.19 (s, 3H, SO_2Me), 3.15 (s, 3H, SO_2Me), 2.22–2.17 (m, 1H, $C_{6b}H$), 2.08–1.98 (m, 1H, $C_{6a}H$), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.2, 81.1, 79.0, 77.5, 67.5, 53.7, 51.5, 45.3,

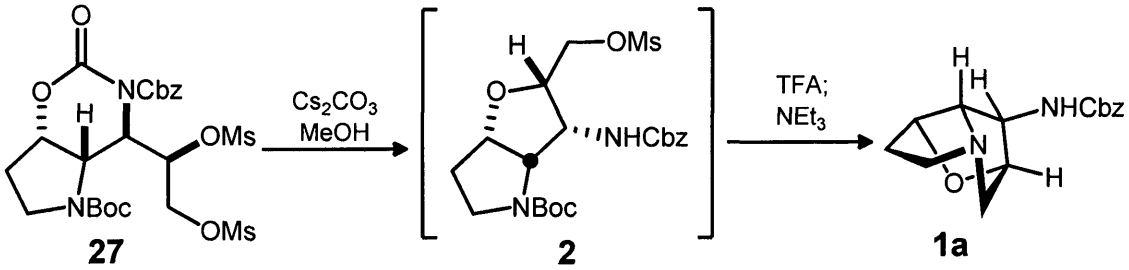
39.2, 38.0, 32.3, 28.6; HRMS (ES+): Exact mass calcd for $C_{15}H_{26}N_2O_{10}S_2Na^+$ $[M+Na]^+$, 481.0927. Found 481.0921.



23 **24**

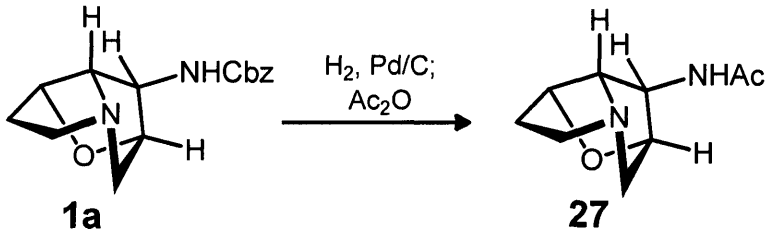
Synthesis of Imide (24). To a solution of compound **23** (0.180 g, 0.39 mmol) in THF (4.0 mL) was added DMAP (0.063 mL, 0.51 mmol, 1.3 equiv), NEt_3 (0.156 mL, 1.12 mmol, 2.8 equiv), and CbzCl (0.137 mL, 0.96 mmol, 2.4 equiv) dropwise over 15 min. The reaction mixture was stirred for 3 h at 23 °C. The reaction was charged with an additional portion of NEt_3 (0.156 mL) and CbzCl (0.137 mL). After stirring an additional 3 h, the reaction mixture was poured into a separatory funnel containing 0.1M HCl (15 mL) and extracted with $CHCl_3$ (2 x 20 mL). The combined organic portions were then washed with saturated $NaHCO_3$ (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting cloudy oil was purified by flash chromatography on silica gel (elution: 50→100% EtOAc in hexanes) to afford **31** (0.222g, 96% yield) as a colorless solid: mp 99–102 °C; TLC (100% EtOAc), R*f*: 0.70 (ninhydrin); IR (film) 3025, 2977, 2938, 2356, 1799, 1700, 1685, 1404, 1175, 928, 755cm^{-1}; NMR spectrum of **24** was complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 5H, Ph), 5.35–5.21 (m, 2H, PhC_1R), 5.17 (m, 1H, C_2H), 5.09 (m, 1H, C_8H), 5.01 (m, 1H, C_1H), 4.48–4.37 (m, 2H, C_3H), 4.35 (m, 1H, C_7H), 3.90–3.68 (m, 1H, $C_{5b}H$), 3.29–3.21 (m, 1H, $C_{5a}H$), 3.17–3.15 (m, 3H, SO_2Me), 2.99 (s, 3H, SO_2Me), 2.26–2.21 (dd, J_1 = 5.9 Hz, J_2 = 6.3 Hz, 1H,

$C_{6b}H$), 2.13 (m, 1H, $C_{6a}H$), 1.45–1.41 (m, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 153.9 153.5, 152.9, 147.1, 134.5, 128.6, 128.5, 128.0, 127.7, 82.0, 81.4, 80.9, 80.7, 77.2, 75.9, 75.4, 69.9, 69.6, 67.0, 66.8, 55.7, 55.3, 55.0, 54.5, 44.7, 44.4, 39.0, 38.8, 37.5, 32.5, 28.1; HRMS (ES+): Exact mass calcd for $C_{23}H_{32}N_2O_{12}S_2Na$ $[M+Na]^+$, 615.1289. Found 615.1296.



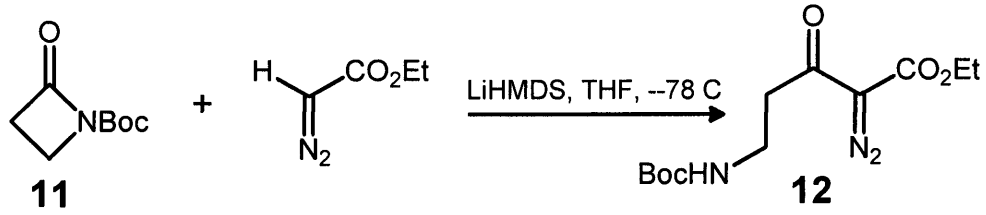
Cbz-norloline (1a). To a solution of compound **27** (1.51 g, 2.57 mmol) in MeOH (25.0 mL) was added Cs_2CO_3 (0.502 g, 1.54 mmol, 0.6 equiv). The reaction mixture was stirred at 23 °C for 3 h and the MeOH was removed *in vacuo*. The resulting residue was dissolved in $CHCl_3$ (25 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic portion was removed and the resulting aqueous layer was then extracted with additional $CHCl_3$ (4 x 20 mL). The organic fractions were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography on silica gel (elution: 50→100% EtOAc in hexanes) to afford **2** (0.415 g, 34% yield) as colorless oil and **23** (0.511 g, 45% recovery): TLC (50% EtOAc in benzene), R*f*: 0.40 (CAM). Compound **2** was carried on in the following transformation immediately. Compound **2** (0.415 g, 0.88 mmol) was dissolved in CH_2Cl_2 (15.0 mL), cooled to 0 °C and TFA (4.0 mL) was added dropwise over 5 min. The reaction mixture was allowed to warm to room temperature over 1 h at which time the reaction had gone to completion as

judged by TLC. The reaction mixture was concentrated to dryness under stream of nitrogen gas over 2.5 h. The resulting residue was dissolved in MeOH (10.0 mL) and NEt_3 (1.12 mL, 0.88 mmol, 1.0 equiv) was added. After the stirring for 2 h at 23 °C, the reaction mixture was diluted with $CHCl_3$ (10 mL), poured into a separatory funnel, and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was then extracted with additional $CHCl_3$ (3x 20 mL). The organic fractions were combined, dried (Na_2SO_4) and condensed *in vacuo*. The resulting yellow oil was purified by flash chromatography on silica gel (elution: 0→6% MeOH in $CHCl_3$) to afford **1a** (0.175 g, 99% yield) as a colorless solid: mp = 93–95 °C; TLC (10% MeOH in $CHCl_3$), R*f*: 0.15 (CAM); IR (film) 3177, 2942, 2355, 2330, 1700, 1260, 1019, 961cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.46 (m, *J* = 6.3 Hz, 1H, NRH), 7.26–7.37 (m, 5H, Ph), 5.01 (d, *J* = 12.1 Hz, 1H, $PhCH_a$), 5.10 (d, *J* = 12.1 Hz, 1H, $PhCH_b$), 4.38 (d, *J* = 2.7 Hz, 1H, C_7H), 4.25 (m, *J* = 6.3 Hz, 1H, C_1H), 4.18 (s, 1H, C_2H), 3.36 (m, *J* = 11.7 Hz, 1H, $C_{3a}H$), 3.20 (s, 1H, C_8H), 3.03–2.89 (m, 2H, C_5H), 2.35 (m, *J* = 11.7 Hz, 1H, $C_{3b}H$), 2.03–1.95 (m, 1H, $C_{6b}H$), 1.86–1.80 (m, 1H, $C_{6a}H$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 136.1, 128.4, 128.2, 128.1, 80.8, 74.0, 69.4, 66.8, 60.9, 58.6, 54.2, 33.0; HRMS (ES+): Exact mass calcd for $C_1H_{18}N_2O_3Na^+$ $[M+Na]^+$, 297.1210. Found 297.1209.



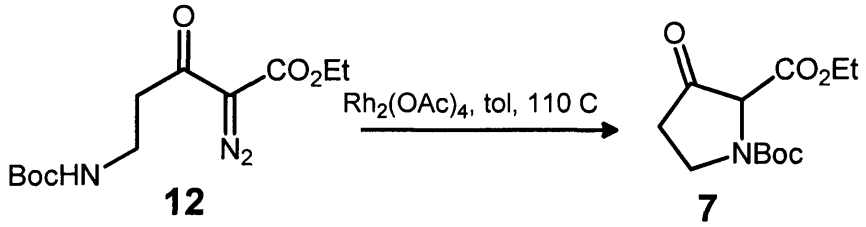
Acetylnorloline (27). To a solution of compound **1a** (0.015 g, 0.05 mmol) in a 1:1 mixture MeOH/EtOAc (3mL) was added 5% Pd/C (0.015 g). The reaction mixture vessel was flushed with hydrogen was bubbled through the stirring solution for 20 min. The reaction mixture was then stirred under a balloon of hydrogen until TLC indicated complete consumption of starting material (40 min). The reaction mixture was purged with N_2 and diluted with additional 1:1 MeOH/EtOAc (7 mL) and filtered through a plug of celite. The plug was washed with additional MeOH/EtOAc (40 ml) and concentrated *in vacuo*. The resulting residue was taken up in $CHCl_3$ and Ac_2O (0.020 mL) was added to the stirring solution. After TLC indicated reaction completion (16 h), the solvent was removed *in vacuo*. To the residue was added 1M NaOH solution (5 mL) and the reaction mixture was stirred for 15 min before dilution with $CHCl_3$ (10 mL) and transfer to a separatory funnel. The organic layer was removed and the aqueous phase was extracted with additional $CHCl_3$ (3 x 5 mL). The organic portions were combined, dried (Na_2SO_4), and concentrated *in vacuo* to afford **27** (7 mg, 71% yield) as a colorless oil; TLC (10% methanol in chloroform), R*f*: 0.15 (CAM); IR (film) 2931, 2856, 2360, 1675, 1540, 1296, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48–4.46 (dd, J_1= 1.9 Hz, J_2= 4.4 Hz, 1H, C_7H), 4.44 (m, 1H, C_1H), 4.18 (m, 1H, C_2H), 3.33–3.30 (d, J = 11.9 Hz, 1H, $C_{3a}H$), 3.12 (m, 1H, C_8H), 3.15 3.10 (m, J = 3.5 Hz, 1H, $C_{5b}H$), 2.89 (m, J_1 =12.8 Hz, J_2 = 9.4 Hz, 1H, $C_{5a}H$), 2.46–2.43 (d, J = 12.1 Hz, 1H, $C_{3b}H$), 2.14–2.02 (m, 2H, C_6H), 1.99 (s, 3H,

OCMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.29, 80.96, 73.75, 69.67, 60.94, 57.56, 54.61, 33.87, 23.21 ; HRMS (ES+): Exact mass calcd for $C_9H_{14}N_2O_2Na^+$ $[M+Na]^+$, 205.0947. Found 205.0940.



Ethyl 5-((*tert*-butoxycarbonyl)amino)-2-diazo-3-oxopentanoate 12. To a solution of ethyl diazoacetate (62 mg, 0.068 mL, 0.65 mmol, 2 equiv) and **11**[2] (56 mg, 0.32 mmol) in THF (3.0 mL) at –78 °C was slowly added LiHMDS (0.65 mL, 0.65 mmol, 1.0 M in THF, 2.0 equiv) over 1 h *via* syringe. After 2 h, the reaction was quenched with saturated NH_4Cl (35 mL). The mixture was extracted with Et_2O (3 x 30 mL). The combined organic portions were washed with brine (35 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (elution 10% → 50% EtOAc in hexanes) to afford **12** (120 mg, 80% yield) as a bright yellow oil: TLC (20% EtOAc in hexanes), R*f*: 0.25 (UV, CAM); IR (film) 3394, 2980, 2936, 2408, 2138, 1732, 1651, 1511, 1073, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) □5.08(br. s, 1H, NRH), 4.16 (q, *J*= 7.0 Hz, 2H, EtO), 3.30 (m, *J* = 5.8 Hz, 2H, $RNCH_2$), 2.91 (t, *J* = 5.9 Hz, 2H, CH_2), 1.28 (s, 9H, *t*-Bu), 1.19 (t, *J* = 7.03 Hz, 3H, EtO); ^{13}C NMR (100 MHz, $CDCl_3$) □191.4, 160.8, 155.4, 78.6, 75.9, 61.2, 40.4, 35.2, 28.0, 14.0.

[2] *N*-Boc-2-azetidinone is both commercially available and can be easily prepared: Chincholkar, P. M.; Kale, A. S.; Gumaste, V. K.; Deshmukh, A., *Tetrahedron* **2009**, *65*, 2605-2609.



12 7

1-*tert*-butyl 2-ethyl 3-oxopyrrolidine-1,2-dicarboxylate (7). To a solution of diazocarbonyl **6** (159 mg, 0.56 mmol) in toluene (11.3 mL, 0.05 M) was added $Rh_2(OAc)_4$ (10.5 mg, 0.015 mmol, 0.04 equiv). The reaction mixture was heated to reflux (110 °C). Additional $Rh_2(OAc)_4$ (10.5 mg, 0.015 mmol, 0.04 equiv) was added every hour for 4 h and then stirred overnight at reflux. The reaction mixture was cooled to 23 °C, filtered through celite, and concentrated *in vacuo* to cleanly afford **7** (80 mg, 55% yield). Compound **7** (prepared by this route) was carried on without purification. Spectral data for **7** matches published data.[10,11]

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CHAPTER III

STUDIES DIRECTED TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF THE LOLIUM ALKALOIDS VIA PETASIS BORONO-MANNICH COUPLING

Introduction and Retrosynthesis:

At the completion of our first generation synthesis of the lolium alkaloids we believed three facets of the route warranted improvement: the high number of synthetic steps, (16 step total), racemic final product, and one low yielding late stage reaction. Even though the loline skeleton is available in four steps from the TA reaction product (Chapter II), construction of the TA substrate required over twelve synthetic steps. Failure of the enantioselective enzymatic Baker's yeast reduction to afford starting material in appreciable yield did not allow for asymmetric synthesis. In addition, one of the final alkylations yields less than 35% of desired product (but 43% of the precursor, Chapter II, **Scheme 2.6**), preventing preparation of the final product on a multi-gram scale.

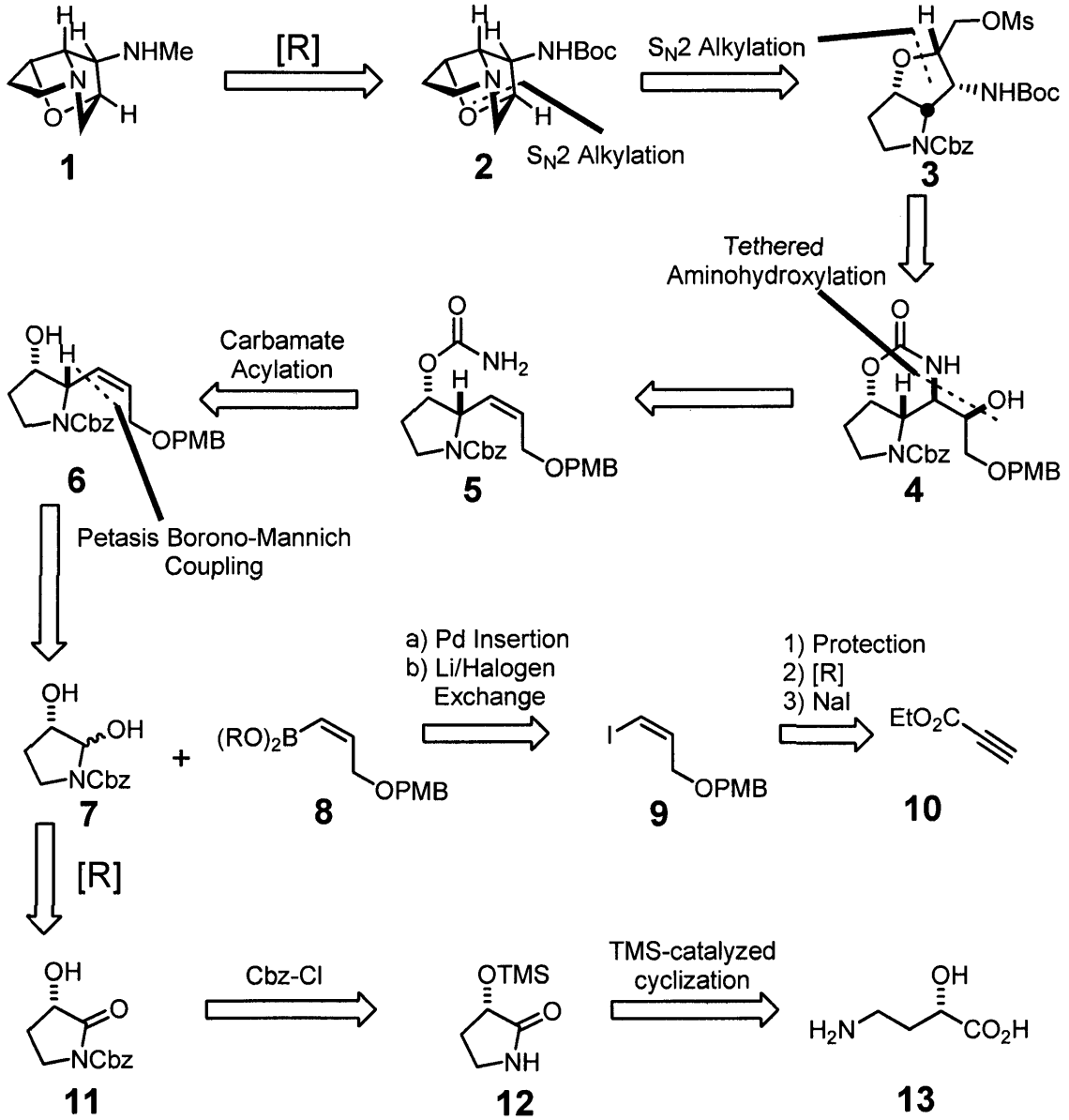
To streamline the synthesis of the TA substrate, identification of more powerful disconnections was required. We hypothesized that a more efficient route to the *Z*-olefin substituted pyrrolidine framework could be achieved by the Petasis Borono Mannich coupling. Initiating the synthesis from enantiopure starting material would circumvent enzymatic asymmetric induction. Previously, we found high regioselectivity for endocyclic cleavage of the Boc-derived imide (Chapter II) as well as Rojas and

co-workers.[1] Therefore, in a second generation synthesis, we desired a Boc derivative from the TA reaction product. [1,2]

With these improvements in mind, we designed a second generation synthesis. **Scheme 3.1** displays our retrosynthesis of this new route. The first four disconnections **1–4** are almost identical to the first generation synthesis (Chapter II). Loline **1** is predicted to arise from the Boc-protected **2** through simple reduction of the carbamate to the methylamine function. Loline skeleton **2** is predicted to follow from TA product **4** upon converting the hydroxy groups to mesylates, activation of the cyclic carbamate with Boc, and subsequent carbonate catalyzed methanolysis/alkylation to intercept bicycle **3**. Hydrogenation exposes the secondary amine to the pendant mesylate to afford **2**. Intermediate **4** is traced back to the carbamate **5** by tethered aminohydroxylation (TA) because **5** differs from the prior successful TA substrate (Chapter II) by only the addition of PMB allylic ether and Cbz instead of Boc protecting group.[3-6]

The largest deviation from our first route occurs in the synthesis of TA precursor, carbamate **5**. We predicted that carbamate **5** could be prepared from alcohol **6** exposure of the hydroxy group to trichloro acetylisocyanate. We envisioned circumventing unnecessary steps by synthesizing olefin **6** from diol **7** and boronate **8** by a modified Petasis Borono-Mannich (PBM) coupling reaction.[7,8] The modified PBM is a substrate-directed addition of vinyl boronates to acyliminium ions and can be used to diastereoselectively prepare functionalized pyrrolidines and piperidines.[7,8] Explanation of this reaction will follow. With strong precedent for the PBM coupling, we switched our attention to devise a route to the necessary coupling partners.

Scheme 3.1: Second generation retrosynthesis to loline



We traced **7** back to **13** through a concise, three step route. With literature precedent, we predicted diol **7** could arise from the reduction of the lactam carbonyl of pyrrolidine **11**. We anticipated facile acylation of lactam **12** *via* lithiation. Subsequent acidic workup would remove the silyl ether protecting group affording hydroxy pyrrolidine **11**. Previously pyrrolidine **12** was prepared from **13** *via* a TMS catalyzed peptide coupling with commercially available (*S*)-4-amino-2-hydroxybutyric acid.[9]

Synthesis of vinyl boronate **8** proved more challenging than pyrrolidine **7**. Though vinyl boronate esters may be synthesized in one step from alkynes by Rhodium catalyzed borylation, the required reagents are difficult to handle.[10,11] We hypothesized that either lithium/halogen-exchange/borylation or palladium catalyzed reactions with vinyl iodide **9** could prepare boronate **8**. The vinyl alcohol of **9** has previously been synthesized so we predicted **9** to arise from **10** through sequential conjugate addition of sodium iodide, Dibal reduction, and *para*-methoxybenzyl ether formation to afford desired substrate **9**.[12]

Our second generation synthetic plan addresses the three major limitations of our first route. TA substrate **5** can hypothetically be prepared in five steps from enantiopure starting material, drastically reducing the number of overall steps. Enantiopure starting material allows for the asymmetric synthesis of loline, overcoming our inability to induce asymmetry in the previous route (Chapter II). Reversing the location of the Boc and Cbz amine protecting groups would increase the regioselectivity of the required cyclic carbamate methanolysis.

Petasis Borono-Mannich Background Information:

In 1993, Petasis and co-workers reported a modified mannich reaction in which vinyl boronic acids served as the nucleophile.[13-17] This coupling was thereafter referred to as the Petasis Borono-Mannich (PBM) reaction. The original communication showcased the condensation of a secondary amine with paraformaldehyde followed by addition of a boronic acid (**Figure 3.1**).[17] Although the exact mechanism remains unclear, it is generally thought that the amine attacks the carbonyl, forming a transient amino alcohol which coordinates with the electrophilic boron leading to an "ate"-complex (**Figure 3.2**). Subsequent vinyl transfer affords the allylic amine.

Figure 3.1: General mechanism of the Petasis Borono-Mannich reaction

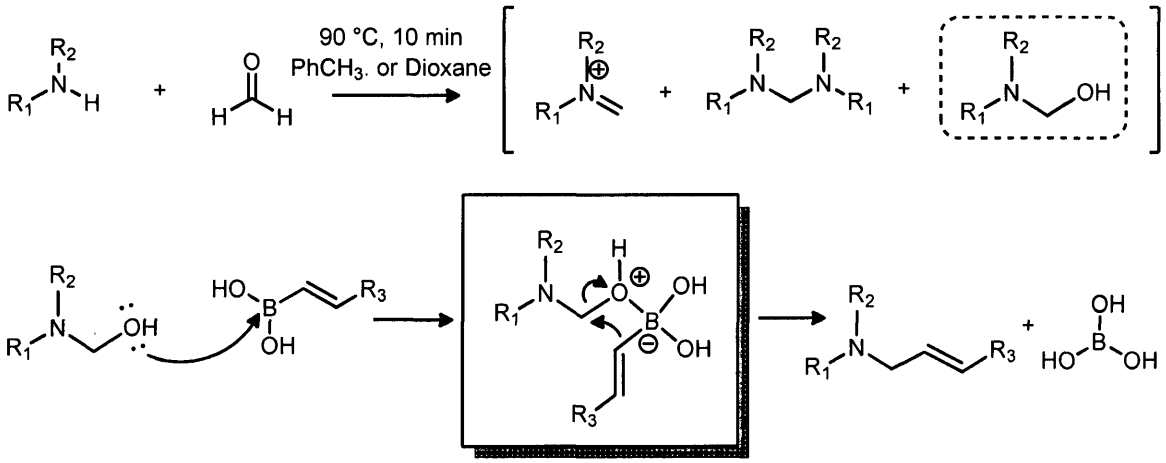
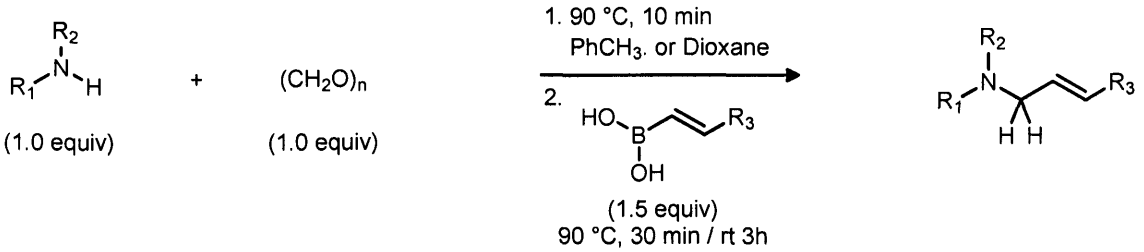
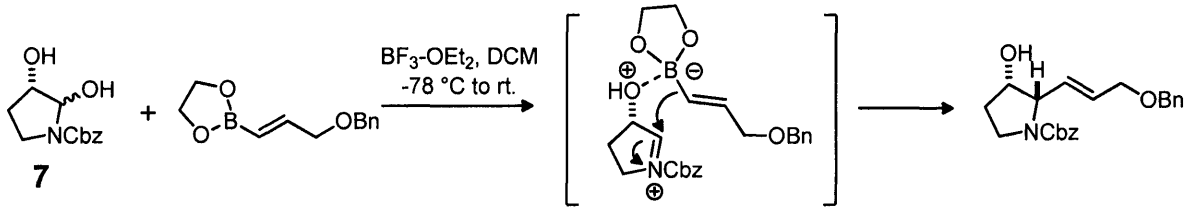


Figure 3.2: General Petasis Borono-Mannich reaction scheme



Even though Petasis has shown the reaction does not traverse through an iminium ion intermediate, Batey and co-workers reported a variant of the PBM that proceeds through an acyliminium ion intermediate formed under lewis acidic conditions.[7,8] They hypothesized that Cbz-protected diol pyrrolidine **7** (**Figure 3.3**) could form an acyliminium ion *in situ*. The substrate would contain a directing pendant hydroxy group and a reactive acyliminium ion center. Not only did Batey and co-workers show that the adjacent hydroxy group is required, but also that the addition of the vinyl boronate occurs stereospecifically because the hydroxy group directs nucleophilic attack.[7] *Syn* addition occurred predominantly with no *trans* product detected.[7]

Figure 3.3: Modified Petasis Borono-Mannich coupling reaction



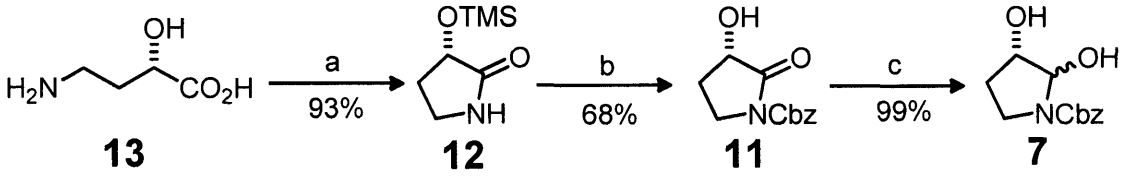
The modified PBM was an obvious disconnection to make in our retrosynthesis because it greatly decreases molecular complexity and introduces a degree of convergency to our strategy. The synthon **8** of our PBM reaction is almost identical to many of the original substrates used originally by Batey.[7] Since Batey reported excellent reactivity for *E*-allylic alcohols and substrates with *Z*-olefin geometry, we anticipated comparable reactivity for the Z-allylic isomer **8** (**Scheme 3.1**).[7,8] With strong precedent for reactivity, the only barrier to the successful coupling would be preparation of the appropriate boronate. Typically, *Z*-vinyl boronates require more steps to prepare than their *E*-counterparts.

Results and Discussion:

At the time of writing, the second generation total synthesis of the lolium alkaloids is not complete, though significant progress toward preparing the coupling partners has been achieved. Several exploratory PBM experiments have been conducted as well. Explanation of the successful synthesis of both compounds and the problems overcome during experimentation follow.

The synthesis of pyrrolidine **7** was successfully accomplished in three steps from (*S*)-4-amino-2-hydroxybutyric acid **12**. **Scheme 3.2** displays our final optimized route. Exposure of amino acid **13** to catalytic TMS-Cl and excess HMDS in refluxing xylene afforded pyrrolidine **12** in excellent 93% yield after flash chromatography. The initial product of the cyclization is bis-silylated pyrrolidine **14.** We found that exposing the crude material to SiO_2 during purification selectively desilylates the amide nitrogen.

Scheme 3.2: Synthesis of the pyrrolidine diol



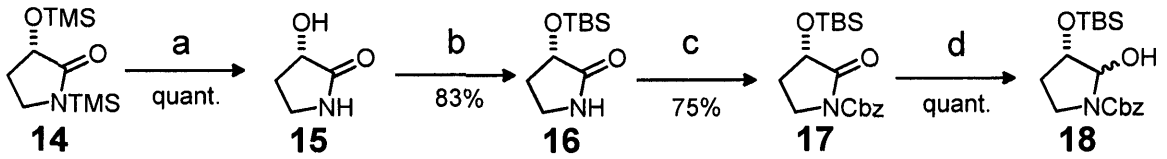
13 **12** **11** **7**

a) TMS-Cl, HMDS, xylene, reflux, 16h; b) LiHMDS (0.95 equiv),THF, CBZ-Cl, -78 °C; c) $NaBH_4$, MeOH , 0 °C.

Even though substrate **12** was readily obtained, subsequent acylation of the amide nitrogen proved difficult. When exposed to triethylamine, catalytic DMAP, and benzyloxychloro formate, lactam **12** lost the silyl ether, resulting in unwanted acylation of the more nucleophilic hydroxy group. Several combinations of related conditions were attempted, but none produced pyrrolidine **11** in any appreciable yield. Exposing

lactam **12** to 0.95 equivalents of LiHMDS at –78 °C successfully lithiated the amide nitrogen. Upon addition of Cbz-Cl, acylation occurred regioselectively and without loss of the silyl ether protecting group. Acidic work-up (1.0M HCl) cleaved the silyl ether affording hydroxy-pyrrolidine **11** in a respectable 68% yield. Reduction of **11** to diol **7** occurred readily in near quantitative yield by exposure to sodium borohydride. Coupling partner **7** was prepared in 63% three step yield from starting material **13**.

Scheme 3.3: Synthesis of TBS protected pyrrolidine diol



a) MeOH, rt, 0.5h; b) TBS-Cl, imid, DMF; c) LiHDMS, THF, CBZ-Cl, -78 °C; d) $NaBH_4$, MeOH, 0 °C.

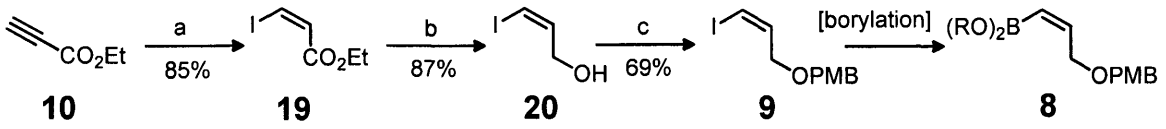
Before we developed our optimized route, several synthetic options were explored. When **12** was first prepared, the bis-silylated product **14** was formed preferentially. We found that an excess of methanol efficiently desilylated both the nitrogen and the oxygen producing the undesired hydroxy lactam **15.** Having **15** in hand presented an opportunity to install the more stable TBS protecting group in place of TMS giving TBS-protected **16**. From **16** the Cbz-protected derivative **17** was synthesized by exposure to identical conditions used to prepare **11**, but without acidic workup. Sodium borohydride provided the facile preparation of dihydroxy **18** from which a test PBM reaction was attempted. No pyrrolidine desired product was formed. We hypothesized that substrate decomposition by Lewis acid occurred preferentially.

Instead of using the mono-silylated dihydroxy **18** as the potential coupling partner, we turned our efforts toward synthesizing **11** from the already prepared **17.**

Exposure to both $BF_3 \cdot OEt_2$ and TBAF resulted in only substrate decomposition. During deprotection with $BF_3 \cdot OEt_2$, starting material was unconsumed after three hours at room temperature. Because the α-hydroxy must be free to coordinate to the boronate during the modified PBM, slow rate of silyl-deprotection is unsatisfactory. TBAF buffered with acetic acid produced **11** in quantitative yield. The slow rate of deprotection of **16** inspired us to develop the concise three step route (**Scheme 3.2**).[7]

With the synthesis of pyrrolidine **7** completed, we shifted attention to preparing vinyl boronate **8.** Commonly, vinyl boronates are prepared by hydroborylation of alkynes, but this methodology furnishes *E*-vinyl boronates instead of the desired *Z*-configuration of **8.** The preparation of *Z*-vinyl boronates from alkynes has been previously reported, but the reagents utilized are not easily prepared and are oxygen sensitive.[10] To overcome this challenge we anticipated vinyl boronate **8** arising from ethyl propionate **10** intercepting vinyl iodide **9**, which in turn would be converted to the boronate *via* lithium/halogen exchange or through palladium catalyzed borylation.

Scheme 3.4: Synthesis of the vinyl boronate



10 **19** **20** **9** **8**

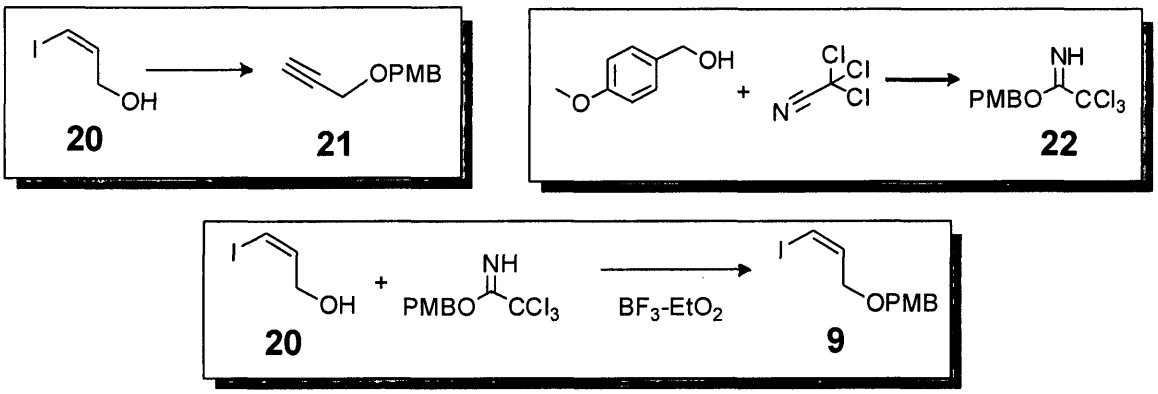
a) NaI, AcOH, reflux, 16h; b) DibalH, DCM, -78 °C; c) PMB-imidate, DCM/Hexanes, BF_3-OEt_2.

Ethyl propionate **10** was exposed to sodium iodide in acetic acid at reflux. Iodide attacks conjugatively at the terminal position of the alkyne. Protonation of the initially formed enol at the position opposite of the iodide affords the desired *Z* product **19** in 85% yield and without further purification. Next, reduction of the ester moiety to the allylic alcohol by DIBAL-H provides vinyl iodide **20** in 87% yield. No conjugate addition was

observed, but the resulting allylic alcohol is difficult to handle (sensitive to decomposition *via* oxygen and light).

Protection of the allylic alcohol with a *para*-methoxybenzyl (PMB) ether was attempted using standard sodium hydride alkylation. Unexpectedly, these conditions produced the undesired β-elimination product, propargyl alcohol **21** (**Figure 3.4**). Alternative conditions were explored, but only gave complex mixture of

Figure 3.4: Preparation of the PMB-protected vinyl iodide

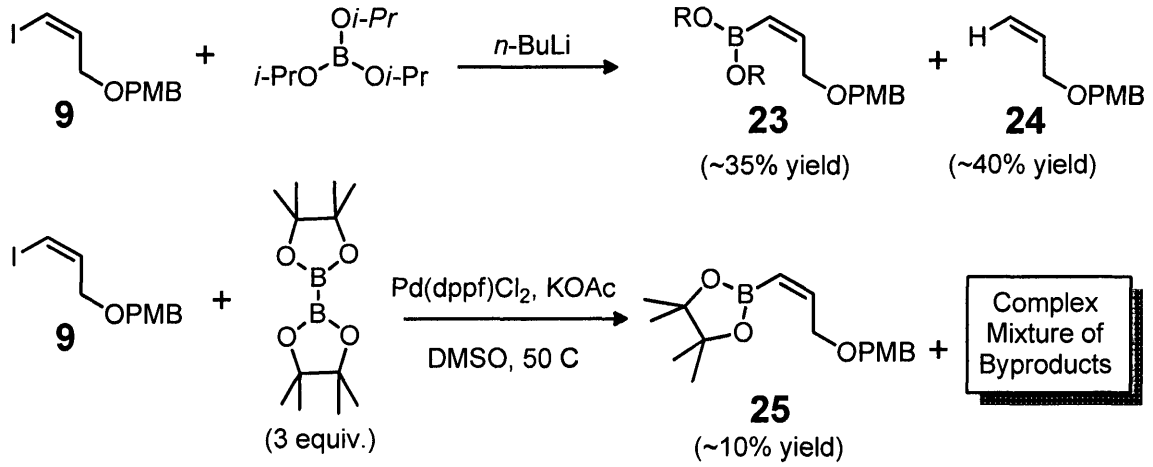


products.[18,19] In order to solve this problem, we prepared the trichloro-PMB-imidate **22** by condensation of *p*-methoxybenzyl alcohol with trichloracetonitrile. Catalytic amounts of $BF_3 \cdot OEt_2$ were used to afford PMB protected vinyl iodide **9** in 69% yield. Residual PMB-OH is difficult to separate from desired product **9** with chromatography, but we ultimately isolated desired product.[20]

Two methods were attempted to prepare boronate **8**. At the time of writing, we lack conclusive evidence for formation of the boronate *via* lithium/halogen exchange. NMR spectroscopy could not conclusively show which boronate isomer was formed, but changes in the chemical shifts of the alkene protons proved that iodine had been replaced

by an atom other than an additional hydrogen. In addition, preliminary results suggest that palladium catalyzed borylation produces desired product.

Scheme 3.5: Preparation of vinyl boronates



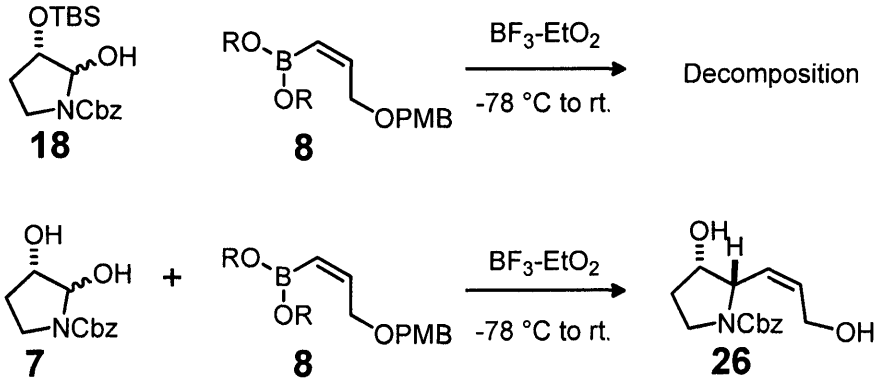
The first method attempted was addition of *n*-butyl lithium to affect lithium/halogen exchange with the vinyl iodide (**Scheme 3.5**).[10] Exposure to triisopropyl borate hypothetically furnishes the isopropyl boronate derivative **23**.[21] Literature precedent reports isopropyl boronates are not stable to moisture and generally do not survive chromatography. Purification was difficult and unproductive. Regardless of precautions taken against exposure to water and oxygen, a significant amount of the deborylated substrate **24** was recovered after each halogen/exchange reaction attempt. We hypothesized that the allylic protons are moderately labile to vinyl lithium deprotonation at temperatures higher than –78 °C.

Due to only limited success of lithium/halogen exchange, palladium insertion/transmetallation was explored.[22] At the time of writing, only exploratory experiments have been conducted. The pinacol boronate **25** was furnished, but in a

complex mixture of products. Presently, we continue effort directed toward producing the desired boronate **8** efficiently.

We attempted the PBM with boronate **8**, (**Scheme 3.6**). From the reaction we recovered TBS derived aminal **18** (as shown in **Scheme 3.3**). Because of our previous

Scheme 3.6: Initial modified PBM experiments and results



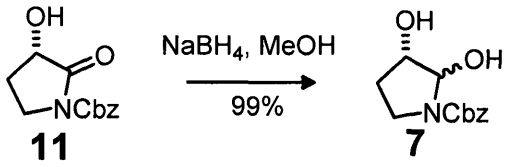
data on TBS deprotection with $BF_3 \cdot OEt_2$ we concluded that the original conditions by Batey and co-workers must be recreated in order to efficiently produce desired product.[7,8] With diol **7** prepared, we again attempted the modified PBM coupling. Diol **26** is the major product of this experiment. Constructive bond formation occurs between the two coupling partners, but the PMB ether is cleaved. Precedent does exist in the literature for cleavage of PMB ethers by nucleophiles under Lewis acidic conditions.[23] Because cleavage of the PMB ether was observed to be slow, we predict that conditions exist to successfully couple diol **7** and boronate **8** without cleaving the PMB protecting group.

Conclusion:

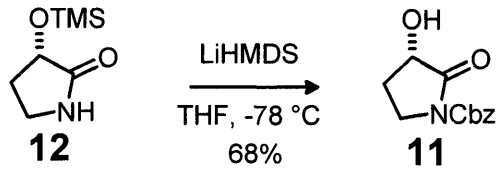
Significant progress toward a successful modified PBM reaction was reported. Multiple challenges were overcome during the course of this research. Overall, we are continuing experiments aimed at furnishing a viable boronate. Once the PBM is optimized, completion of the second generation synthesis will soon follow. In addition, we predict the final route to loline **1** to be ~10 steps, which is a substantial improvement over our first communication.[24] Our revision is on trajectory to correct the three limitations of our first route. To streamline the synthesis of TA substrate **5** our application of the modified PBM reaction is predicted to reduce the route concise five step sequence. As of now, we have induced asymmetry into the route by starting with enantiopure amino acid **13**. Finally, the regioselective cleavage of the proposed cyclic carbamate will be tackled in later stages of the synthesis. With many obstacles overcome, we are confident that with our continuing effort, the second generation synthesis of the lolium alkaloids will be accomplished in due course.

Experimental Section

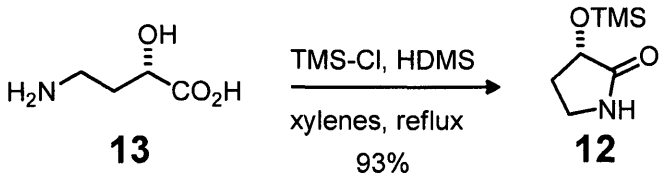
General Information: All reactions were carried out under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring unless otherwise indicated. Acetonitrile, THF, toluene, and Et_2O were degassed with argon and purified by passage through a column of molecular sieves and a bed of activated alumina.[25] Dichloromethane was distilled from CaH_2 prior to use. All reagents were used as received unless otherwise noted. Flash column chromatography[26] was performed using SiliCycle siliaflash P60 silica gel (230–400 mesh). Analytical thin layer chromatography was perfomed on SiliCycle 60Å glass plates. Visualization was accomplished with UV light, anisaldehyde, ceric ammonium molybdate, potassium permanganate, or ninhydrin followed by heating. Film infrared spectra were recorded using a Digilab FTS 7000 FTIR spectrophotometer. Single crystal determinations were carried out using a Bruker *SMART Apex II* diffractometer using graphite-monochromated Cu K radiation. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) spectrometer are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm) or tetramethylsilane (0.00 ppm). The NMR spectra of all compounds containing *t*-butoxy carbonyl (Boc) residues are complicated by carbamate rotamers. Proton-decoupled ^{13}C-NMR spectra were recorded on a Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.00 ppm). All compounds were judged to be homogeneous (>95% purity) by ^{1}H and ^{13}C NMR spectroscopy. Mass spectra data analysis was obtained through positive electrospray ionization (w/ NaCl) on a Bruker 12 Tesla APEX–Qe FTICR-MS with an Apollo II ion source.



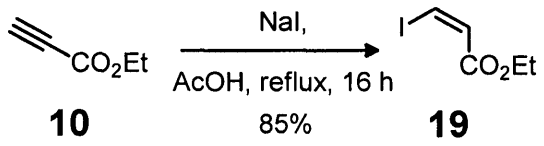
Synthesis of Cbz-protected diol pyrrolidine (7): To a solution of compound **11** (0.020 g, 0.085 mmol) in MeOH (0.70 mL) at 0 °C was added sodium borohydride (0.006 g, 0.043 mmol, 0.5 equiv) in one portion. After stirring 0.5 h at 0 °C, the reaction was quenched with sat. ammonium chloride (2 mL). The organic layer was removed and the aqueous layer extracted with ether (3 x 5 mL). The organic fractions were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting white powder **7** (0.020, 0.084 mmol, 99%) was used without further purification. TLC (60% EtOAc in hexanes), R*f*: 0.40 (UV, CAM); Spectral data for **7** matches published data.[7]



Synthesis of (S)-benzyl 3-hydroxy-2-oxopyrrolidine-1-carboxylate (11): To a solution of **11** (0.112 g, 0.67 mmol) in THF (5 mL) at –78 °C was added LiHMDS (1.0M soln in THF, 0.63 mmol, 0.95 equiv) drop-wise over 5 min. After stirring 0.5 h at –78 °C, CbzCl (0.120 g, 0.70 mmol, 1.05 equiv) was added to the reaction dropwise. The solution was warmed to 23 °C over 1 h and then quenched with 1.0M aqueous hydrogen chloride (10 mL). The reaction mixture was then poured into a separatory funnel, diluted with ethyl acetate (10 mL), and the organic layer removed. The aqueous layer was extracted with additional ethyl acetate (2 x 12 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting white powder was purified by flash column chromatography on silica gel to afford **11** (0.104 g, 66% yield) as a white powder: mp 99.8–100.7 °C; TLC (60% EtOAc in hexanes), R_f: 0.70 (UV, CAM); $[\alpha]_D^{25}$ = – 63.9 (c = 1.94, CH_2Cl_2), IR (film) 3448, 3085, 3028, 2989, 2879, 1778, 1689, 1385, 1282, 1227 cm^{-1}; The spectra of **11** was complicated by amide rotamers ^1H NMR (400 0MHz, $CDCl_3$) δ 7.40 (m, 5H, $C_{Ph}H$), 5.29 (s, 2H, $C_{Bz}H$), 4.38 (m, 1H, C_7H), 3.89 (m, 1H, $C_{5a}H$), 3.60– 3.53 (td, J_1 = 6.6 H z, J_2 = 10.5 Hz, 1H, $C_{5b}H$), 2.48–2.42 (m, 1H, $C_{6a}H$), 2.00–1.94 (m, 1H, $C_{6b}H$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 151.1, 134.9, 128.6, 128.5, 128.2, 77.2, 70.4, 68.3, 42.1, 27.0; HRMS (ES+): Exact mass calcd for $C_{12}H_{13}NO_4Na^+$ $[M+Na]^+$, 258.0737. Found 258.0734

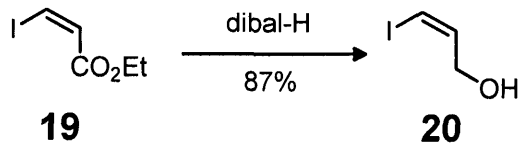


Preparation of (S)-3-((trimethylsilyl)oxy)pyrrolidin-2-one (14): Chlorotrimethylsilane (0.270 mL, 2.1 mmol, 0.05 equiv) was added to a stirred mixture of L(–)-4-amino-2-hydroxy-butyric acid **13** (5.0g, 42.0 mmol), xylene (100 mL), and hexamethyldisilazane (61.5 mL, 294 mmol, 7.0 equiv) at room temperature. The reaction mixture was heated to reflux for 12 h, cooled to room temperature and diluted with absolute ethanol (200 mL). The solvents were removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (340g, elution: 20→100% EtOAc in hexanes) to yield the light brown solid **12** (6.468 g, 89%); TLC (60% EtOAc in hexanes), R_f: 0.25 (UV, CAM); Spectral data for **12** matches published data.[9]



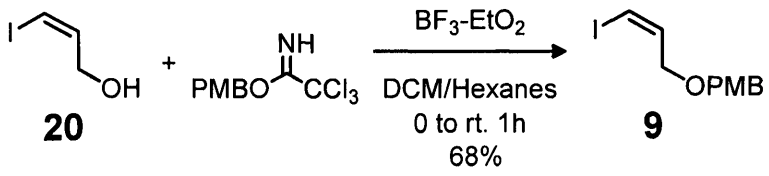
Synthesis of (Z)-ethyl 3-iodoacrylate (19): A two-neck round bottom flask (250 mL) was charged with sodium iodide (16.0g, 111 mmol, 1.5 equiv) and glacial acetic acid (45 mL). To the solution was added ethyl propionate (7.00g, 72 mmol) in one portion. After stirring at reflux (70 °C) for 24h, the reaction mixture was cooled to room temperature and aqueous sodium thiosulfate solution was added (10% *w/w*, 75 mL). The reaction mixture was poured into a seperatory funnel and extracted with ether (3 x 50 mL). A 3.0 M KOH solution (~150 mL) was added slowly to the combined organic extracts (cooled in a ice water bath) until the aqueous layer was pH 7. The aqueous phase was then

removed and the organic layer washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo.* The resulting yellow oil **19** (14.940 g, 92% yield) required no further purification. Spectral data of **19** matches published data.[27]

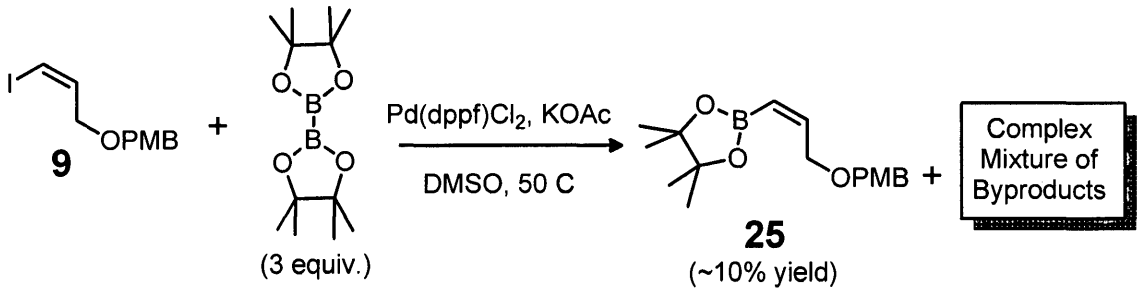


19 **20**

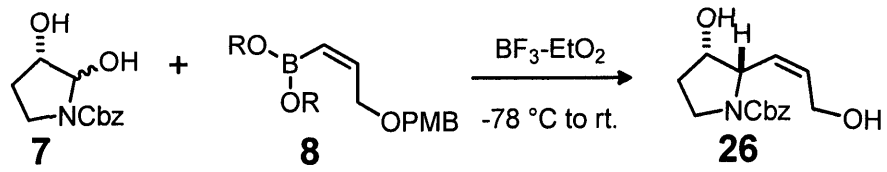
Synthesis of (Z)-3-iodoprop-2-en-1-ol (20): To a solution of **19** (5.6 g, 24.8 mmol) in anhydrous methylene chloride (35.0 mL) at –78 °C was added neat dibal-H (7.04 g, 49.6 mmol, 2.0 equiv). The solution was stirred for 0.5 h at –78 °C and then allowed to warm to rt. over 0.5 h. The reaction mixture was then cooled to –20 °C, diluted with ether (35.0 mL) and quenched with methanol (2.0 mL). A mixture of water and 1.0 M HCl (1:1, 30 mL) was added dropwise. The reaction mixture was then poured into a separatory funnel and the organic layer removed. The the aqueous layer was extracted with ether (3 x 35 mL), the organic extracts were combined, washed with sat. sodium bicarbonate (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography on silica gel (elution: 20→100% EtOAc in hexanes) to yield light yellow oil **20** (3.9 g, 86%) and stored in an opaque flask under nitrogen. TLC (10% EtOAc in hexanes), R_f: 0.35 (UV, CAM); Spectral data of **20** matches reported data.[27]



Synthesis of PMB-protected vinyl iodide (9): To a solution of **20** (1.263 g, 6.86 mmol) in methylene chloride (5 mL) was added PMB-Imidate (1.920 g, 6.86 mmol, 1.0 equiv). The reaction mixture was then cooled to 0 °C. Upon addition of $BF_3{\cdot}OEt_2$ (0.025 mL, cat.) a white precipitate formed which prompted vigorous stirring. After the reaction mixture was warmed to room temperature over 2 h, the reaction was diluted with a mixture of DCM and Hexanes (1:2, 20 mL) and filtered through a plug of celite. The celite was washed with an additional portion of DCM and Hexanes (1:2, 100 mL), and the combined organic fractions were condensed *in vacuo* to afford a light brown solid. The crude material was purifed by flash column chromatography on silica gel (elution: 0%→30% EtOAc in toluene) to afford the pale yellow oil **9** (1.41 g, 68%) and stored in an opaque flask under nitrogen. TLC (40% EtOAc in Hexanes), R_f: 0.60 (UV, CAM); IR (film) 3066, 2932, 2834, 2364, 2335, 1612, 1512, 1456, 1247, 1089, 1034 cm^{-1}; ^1H NMR (400 0MHz, $CDCl_3$) δ 7.31–7.29 (m, 2H $C_{Ph}H$), 6.92–6.90 (m, 2H, $C_{Ph}H$), 6.52–6.47 (dt, J_1 = 5.5 Hz, J_2 = 7.8 Hz, 1H, C_2H), 6.41–6.39 (dt, J_1 = 1.6 Hz, J_2 = 7.8 Hz, 1H, C_1H), 4.48 (s, 2H, $C_{PMB}H$), 4.13–4.11 (dd, J_1 = 1.6 Hz, J_2 = 5.5 Hz, 1H, C_3H), 3.81 (s, 3H, $C_{PhOMe}H$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.2, 129.7, 129.3, 113.6, 83.0, 72.4, 72.1, 55.1; HRMS (ES+): Exact mass calcd for $C_{11}H_{13}IO_2Na^+$ $[M+Na]^+$, 326.9852 Found 326.9859.



Synthesis of pinacol-Boronate (25): To a suspension of $PdCl_2(dppf)$-CH_2Cl_2 (25.0 mg, 0.03 mmol), bis(pinacolato)diboron (759 mg, 3.0 mmol, 3.0 equiv), and KOAc (294 mg, 3.0 mmol, 3.0 equiv) in DMSO (2 mL) was added a solution of vinyl iodide **10** (304 mg, 1.0 mmol) in DMSO (3 mL), and the resulting mixture was heated at 50 °C for 4 h, treated with water (10 mL), and extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (2 x 15 mL), dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the crude (89:10:1 Toluene/EtOAc/Et_3N) afforded 45 mg (10% yield) of **25**. TLC (10% EtOAc in toluene), R_f: 0.5 (UV, CAM); Proton NMR spectral data of **25** (with bis(pinacolato)diboron impurity) is available in **appendix 2**. HRMS (ES+): Exact mass calcd for $C_{17}H_{25}BO_4Na^+$ $[M+Na]^+$, 327.1738 Found 327.1736



Synthesis of diol (26): To a solution of diol **7** (20 mg, 0.080 mmol) and boronate **8** (55 mg, 0.24 mmol, 3.0 equiv) in DCM (1.0 mL) at –78 °C was added dropwise $BF_3{\cdot}OEt_2$ (0.040 mL, 0.32 mmol, 4.0 equiv). The solution was stirred at –78 °C for 2.5 h, warrmed to room temperature and stirred for a further 16 h, extracted with DCM (3 x 15 mL) from $NaHCO_3$ (10 mL satd. Aq), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purifed by flash chromatography (10-100% EtOAc in Hexanes) to afford **26** (15 mg, 68%) as a yellow oil. TLC (50% EtOAc in hexanes), R_f: 0.15 (UV, CAM); Proton NMR spectral data of **26** is available in **appendix 2**. HRMS (ES+): Exact mass calcd for $C_{15}H_{19}NO_4Na^+$ $[M+Na]^+$, 300.1206 Found 300.1205.

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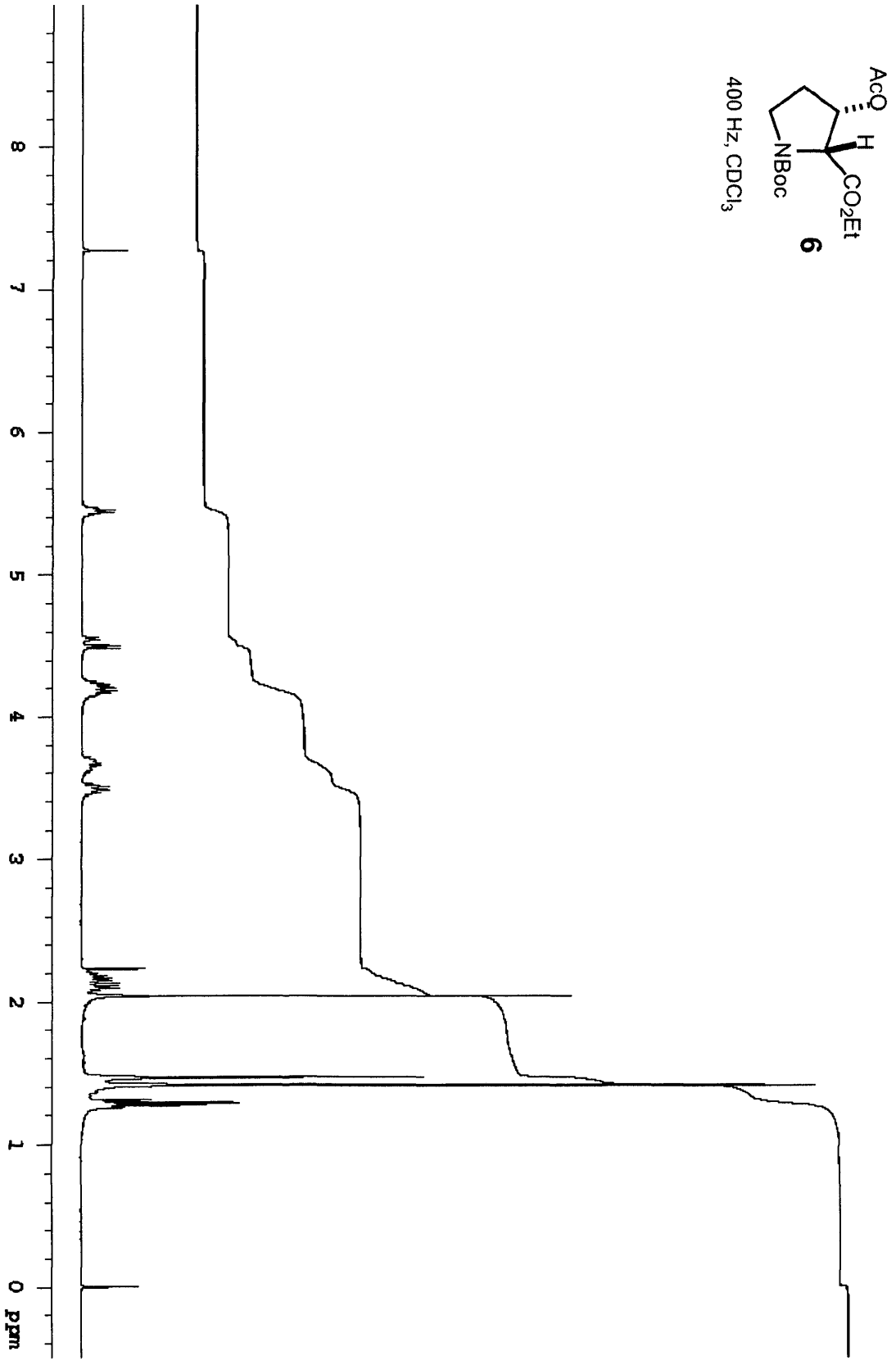
Supporting Information For:

Chapter II: The Total Synthesis of the Lolium Alkaloids *via* Tethered Aminohydroxylation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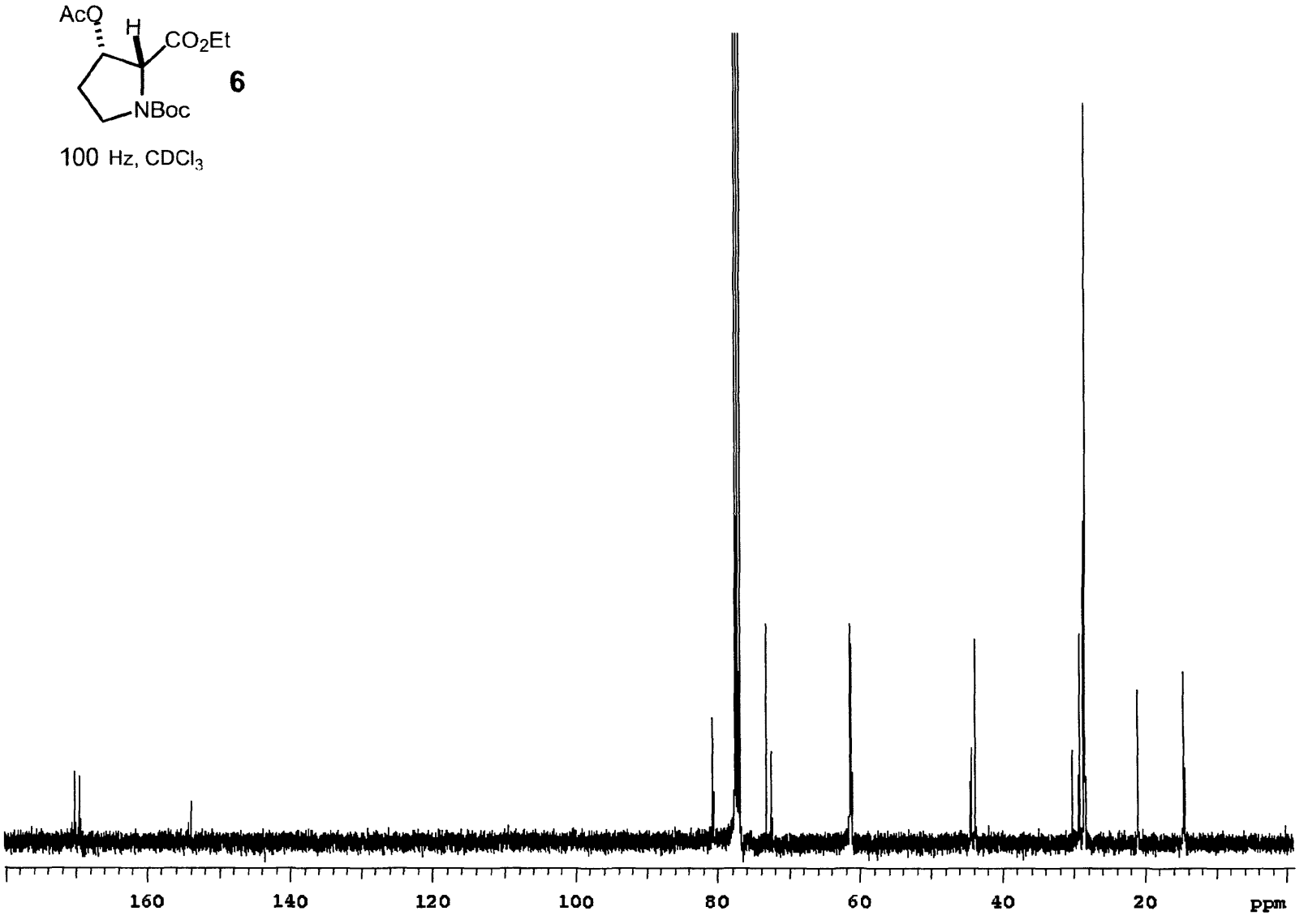
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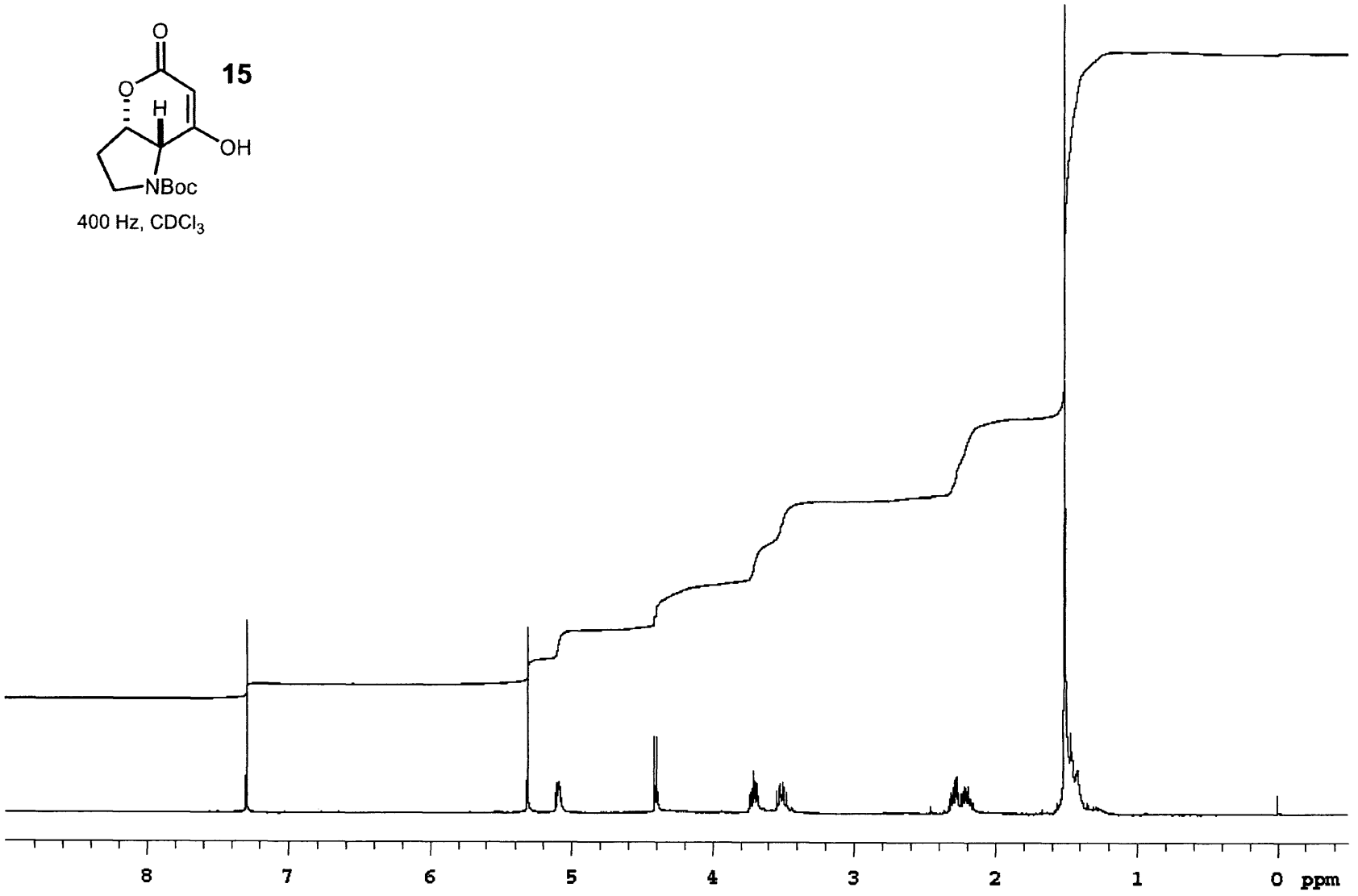
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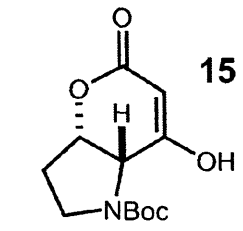

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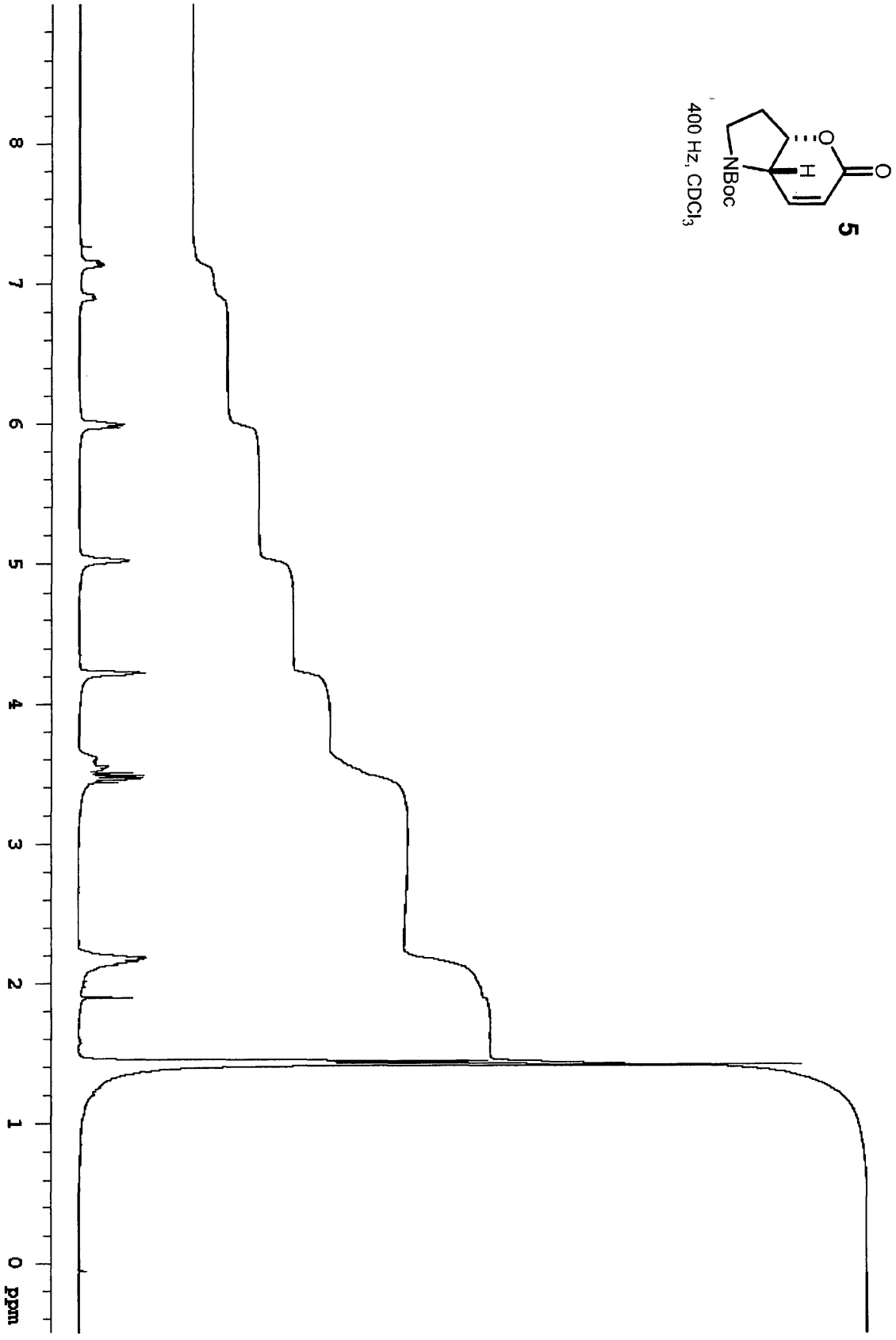
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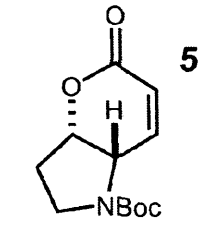
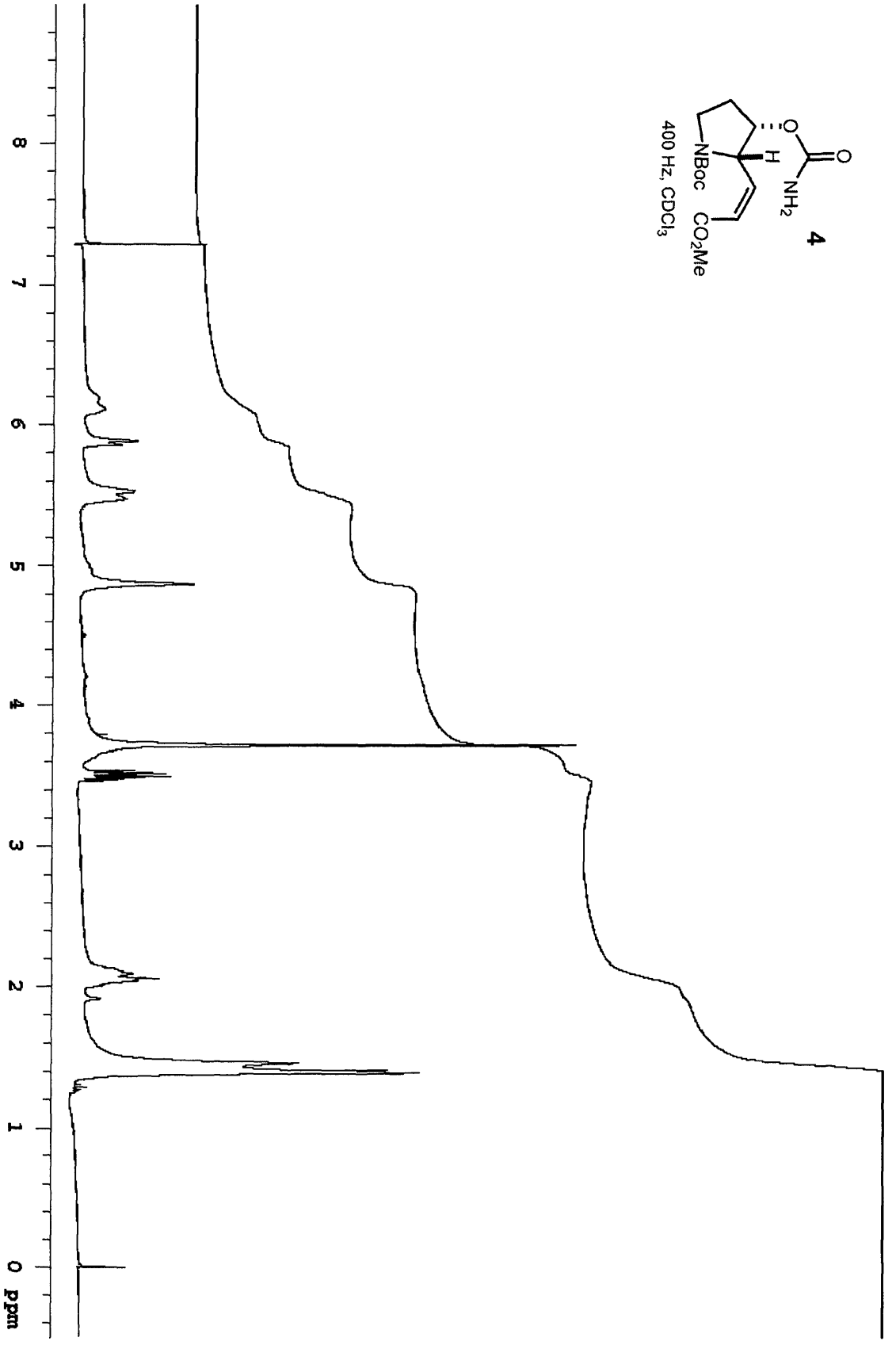
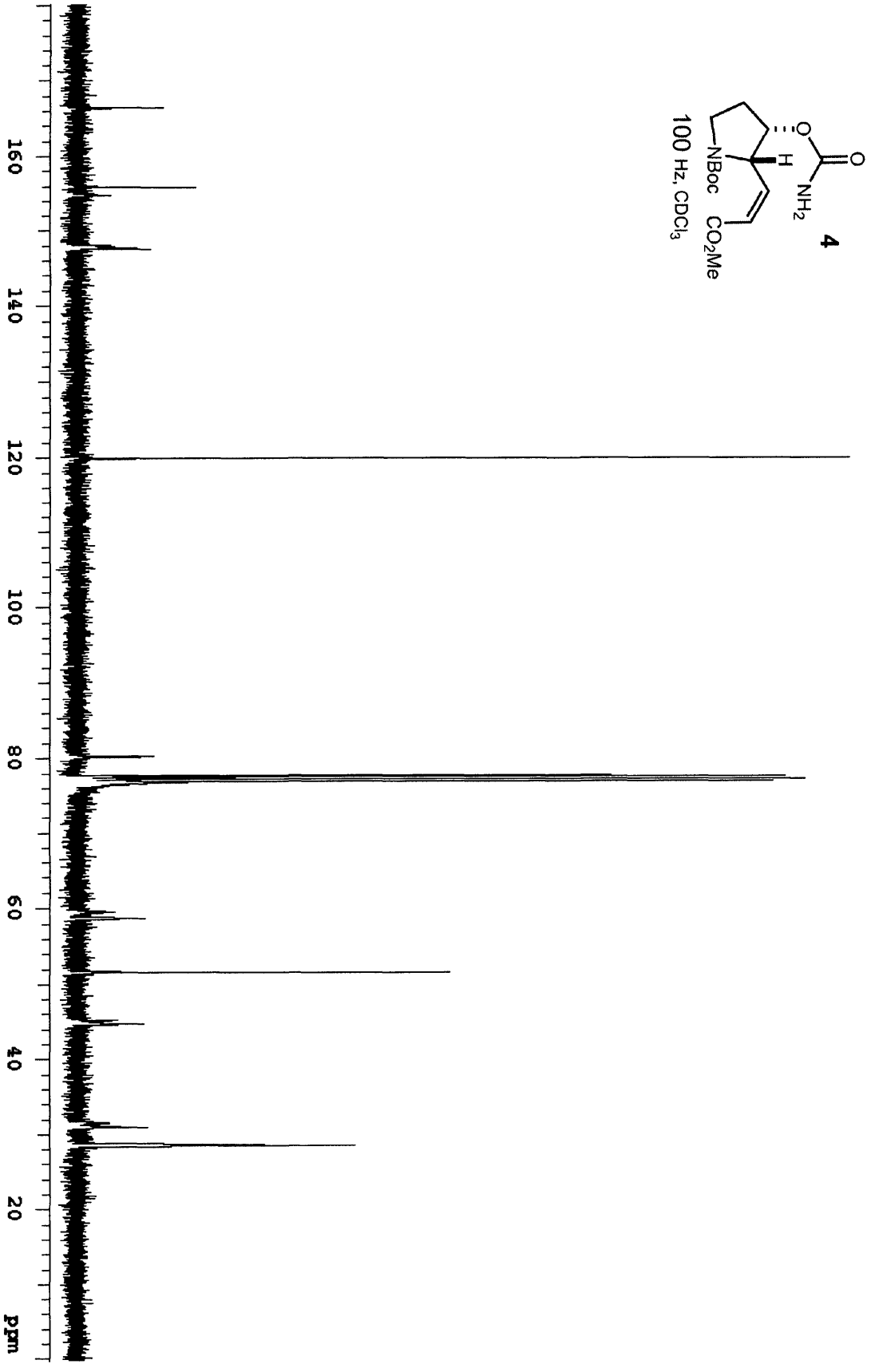
ppm

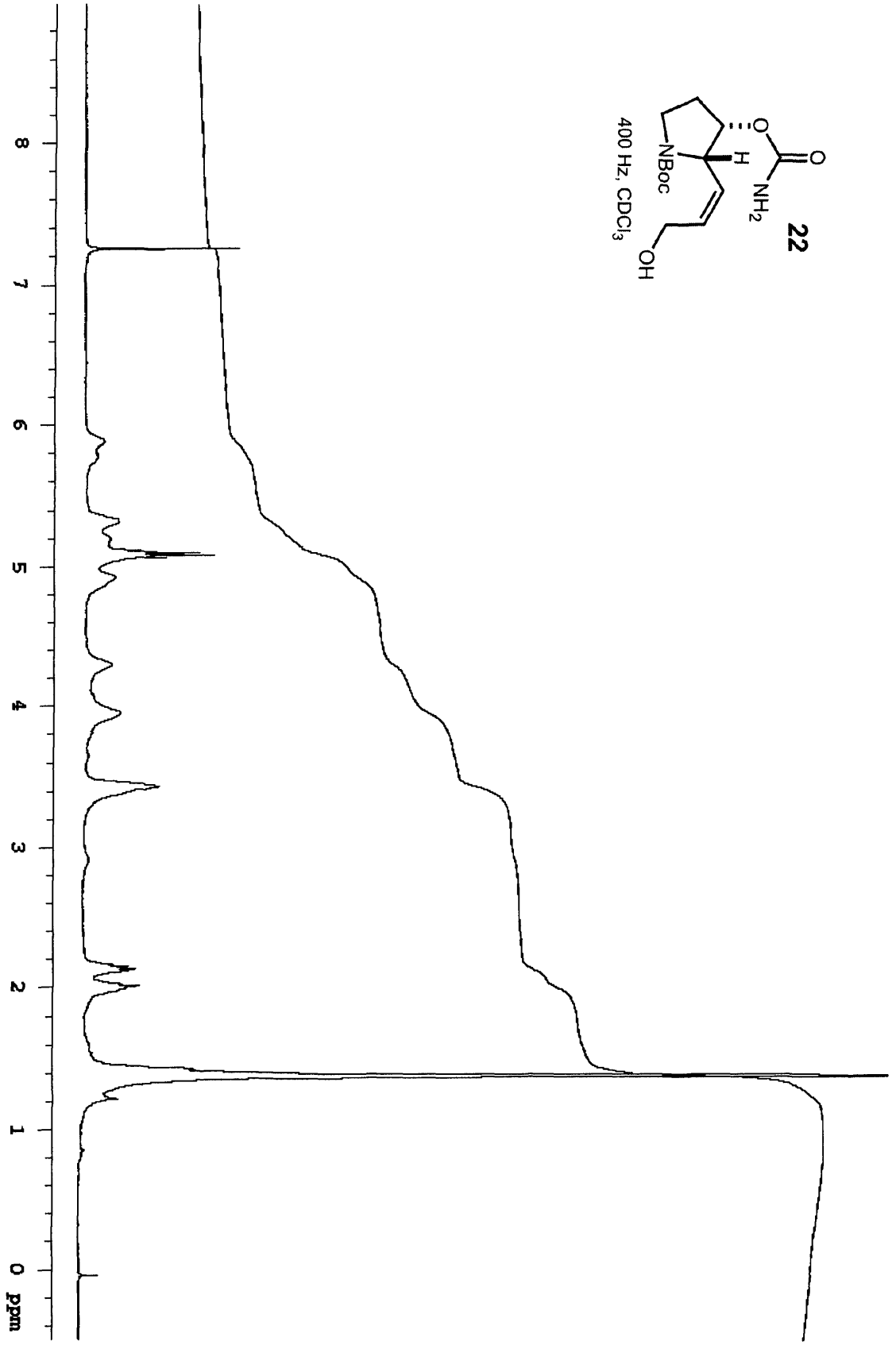


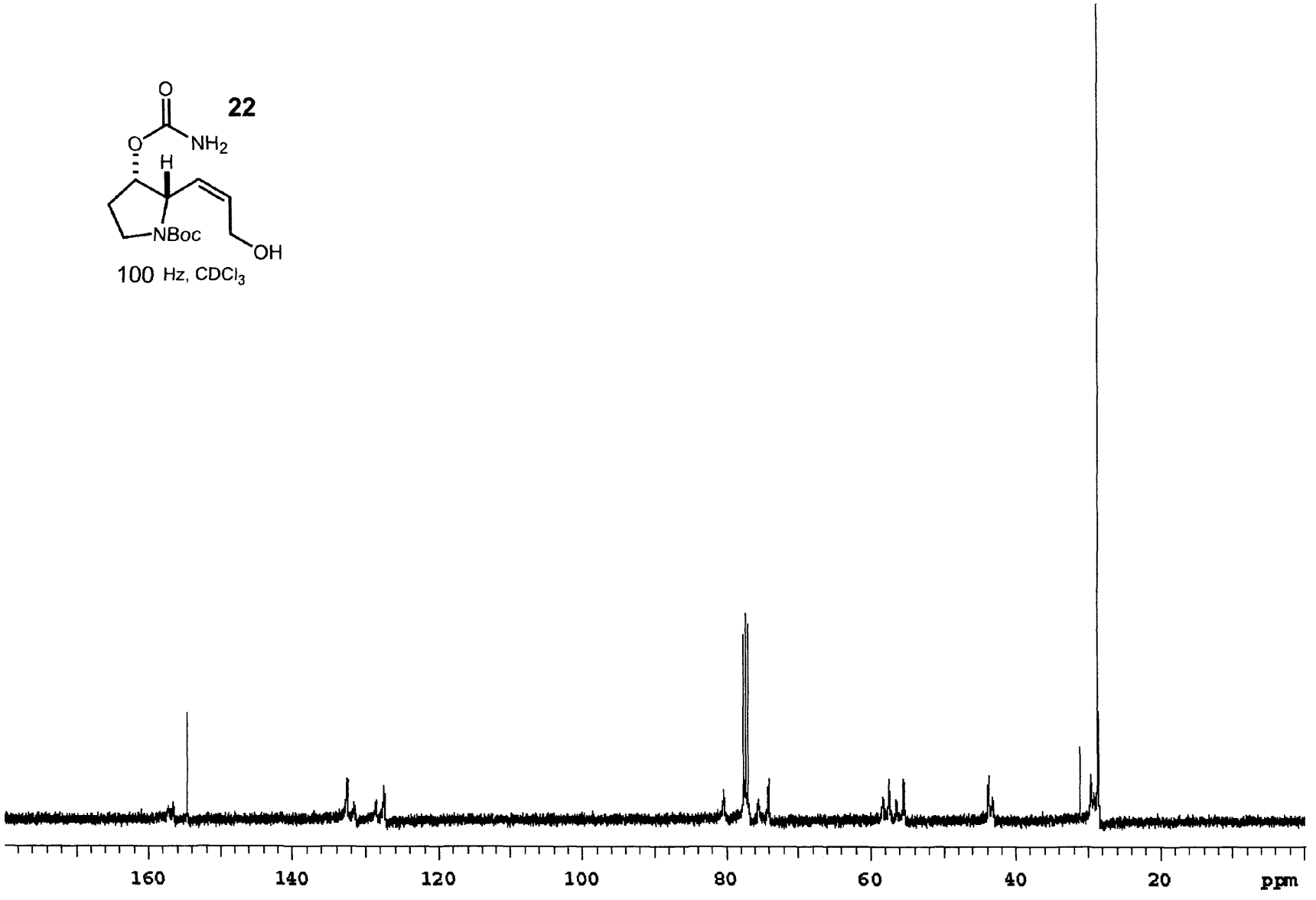
5

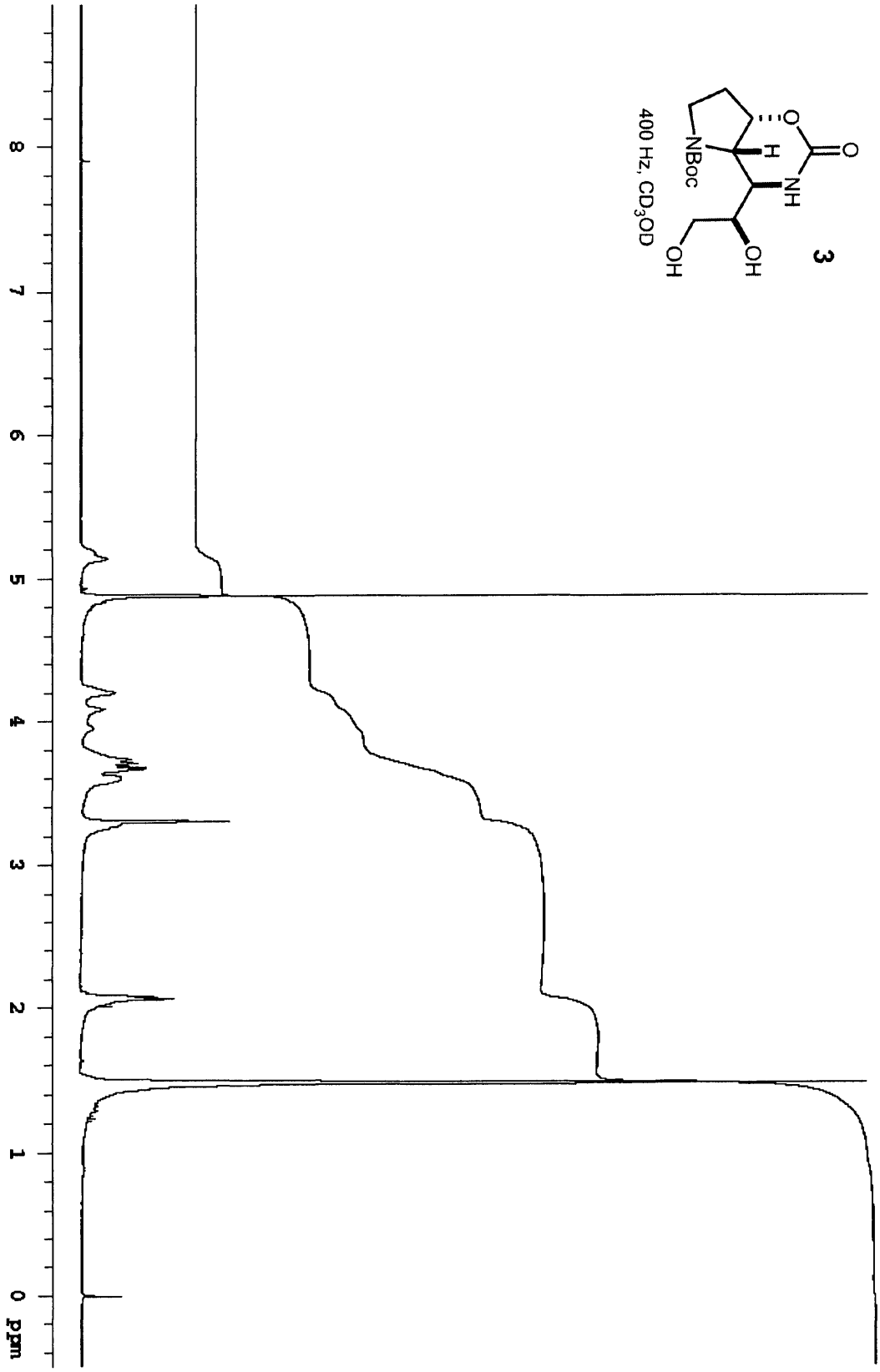
100 Hz, $CDCl_3$

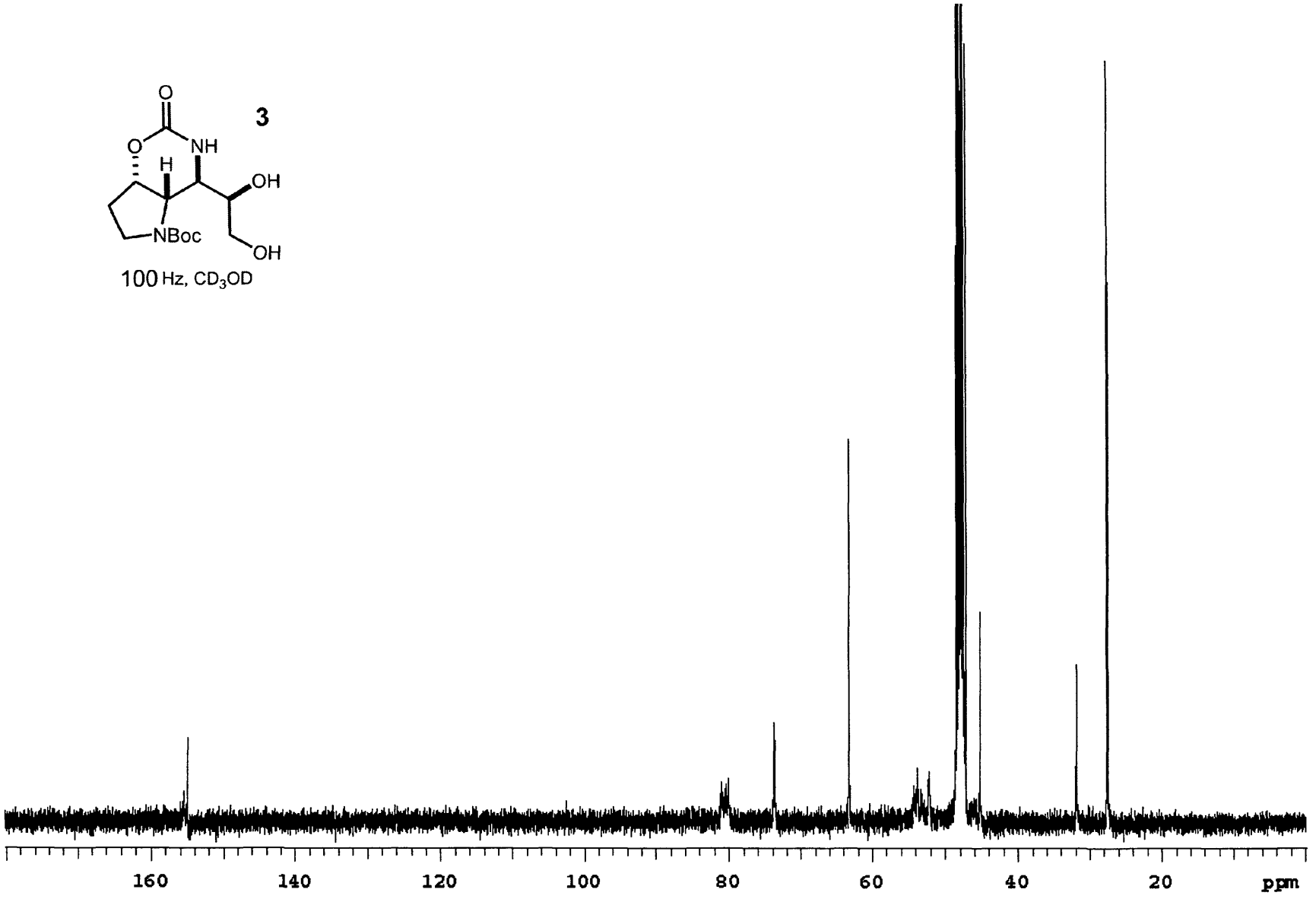

4
NBoc
CO2Me
NH2
400 Hz, CDCl3
8
7
6
5
4
3
2
1
0 ppm

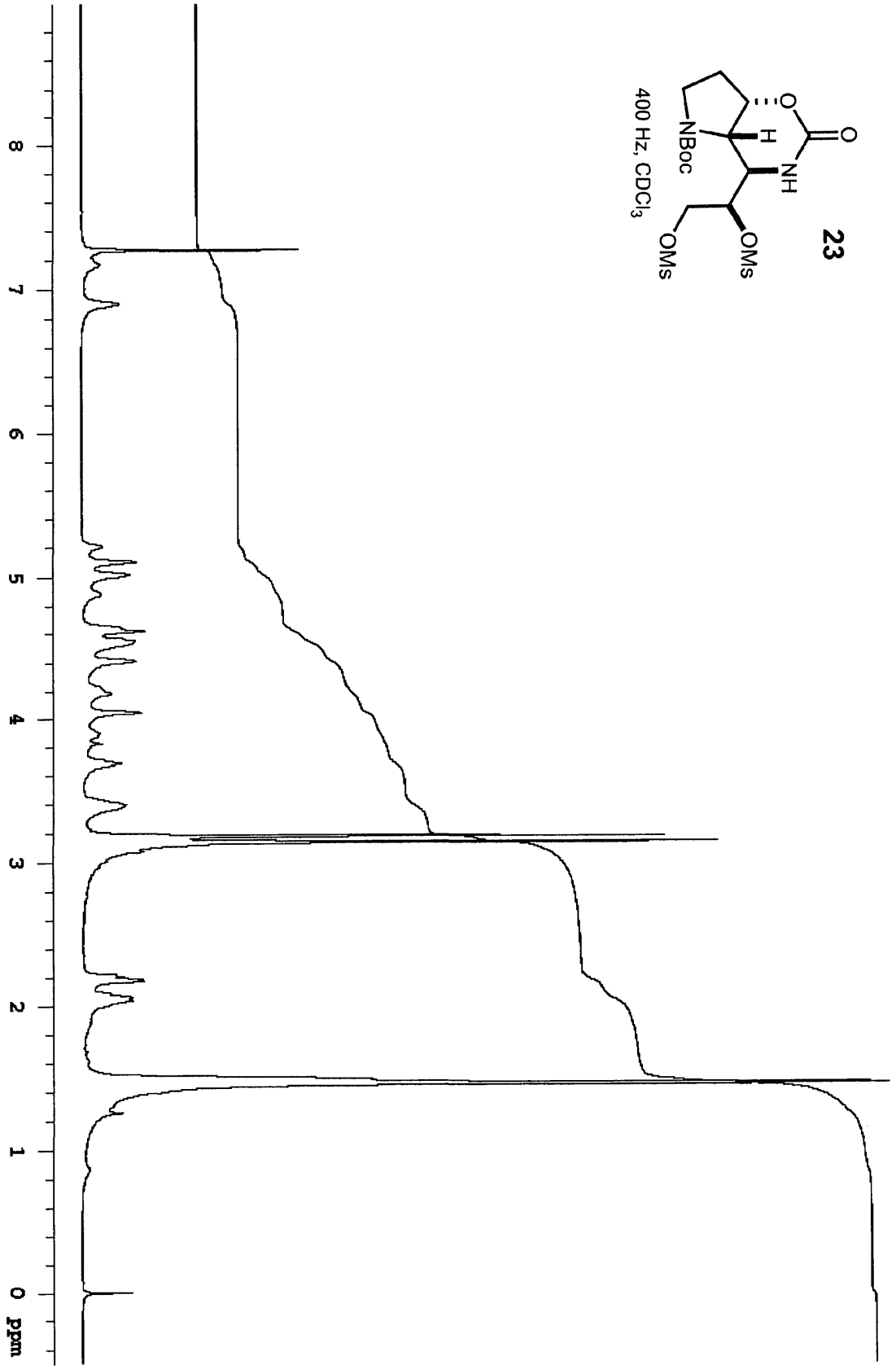

4
100 Hz, CDCl3
NBoc
CO2Me
NH2
O
H
160
140
120
100
80
60
40
20
ppm

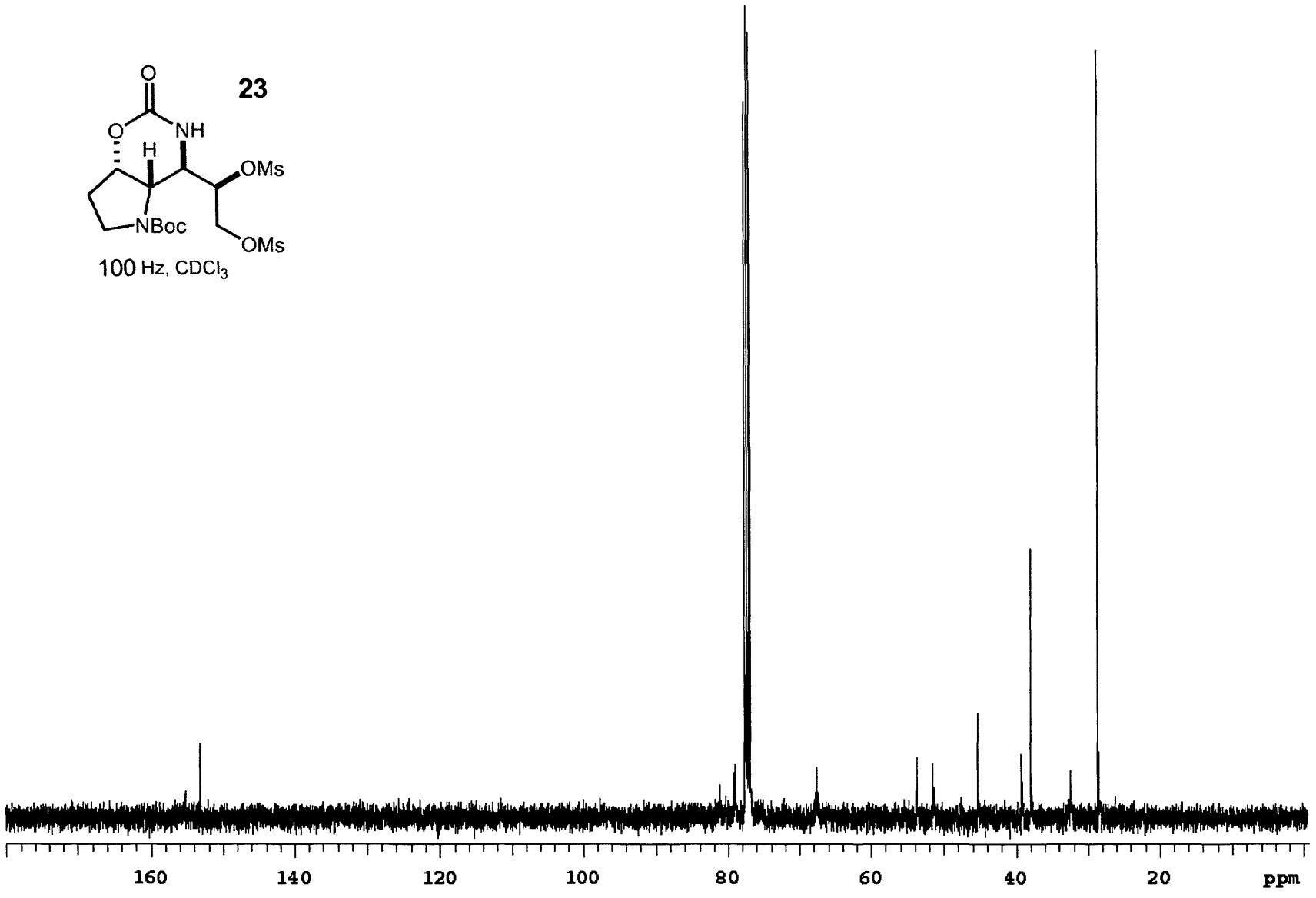

22
400 Hz, CDCl3
NBoc
OH
NH2
O
H
ppm
0
1
2
3
4
5
6
7
8

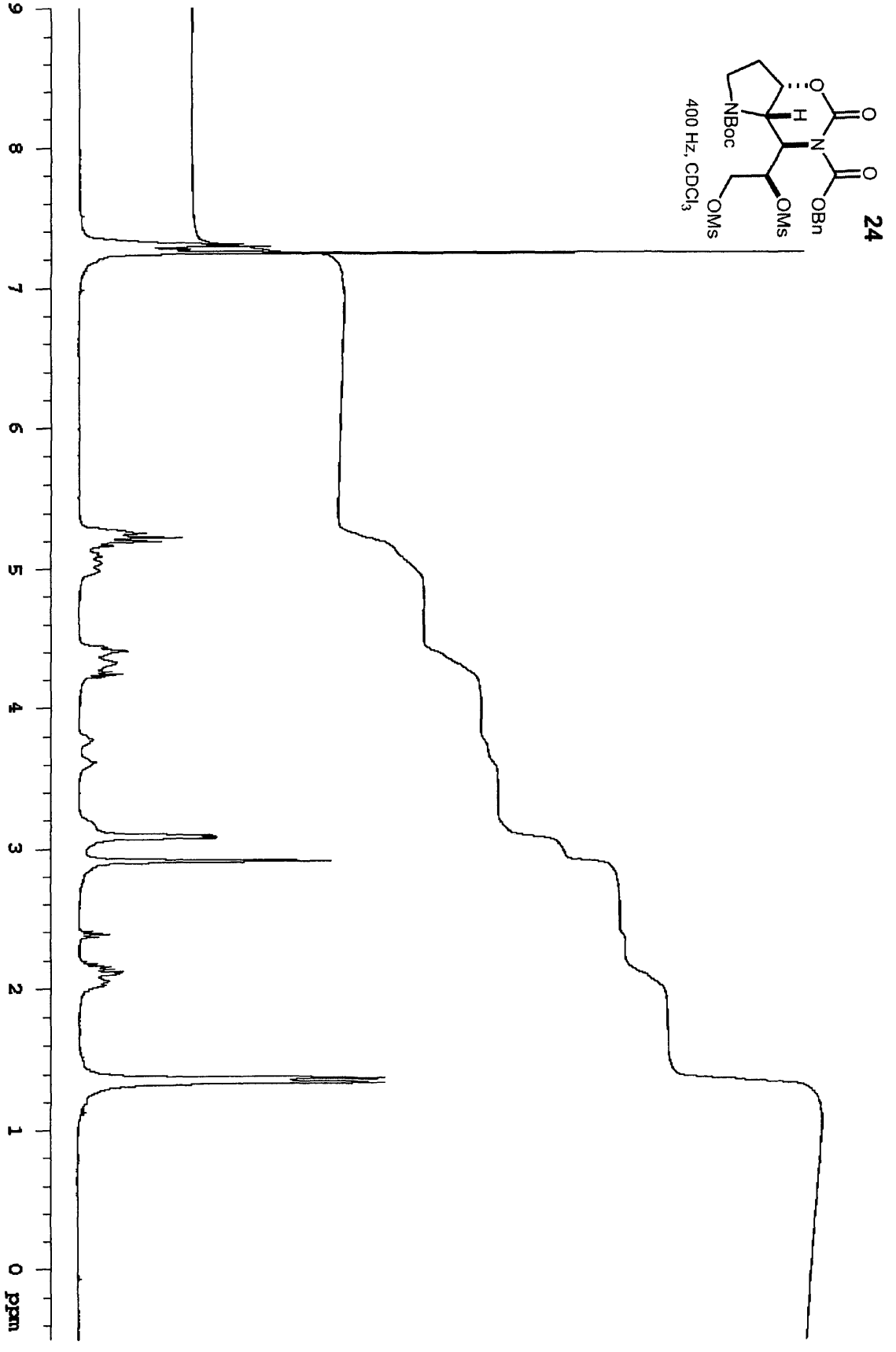

22
O
O
NH2
H
NBoc
OH
100 Hz, CDCl3
160
140
120
100
80
60
40
20
ppm

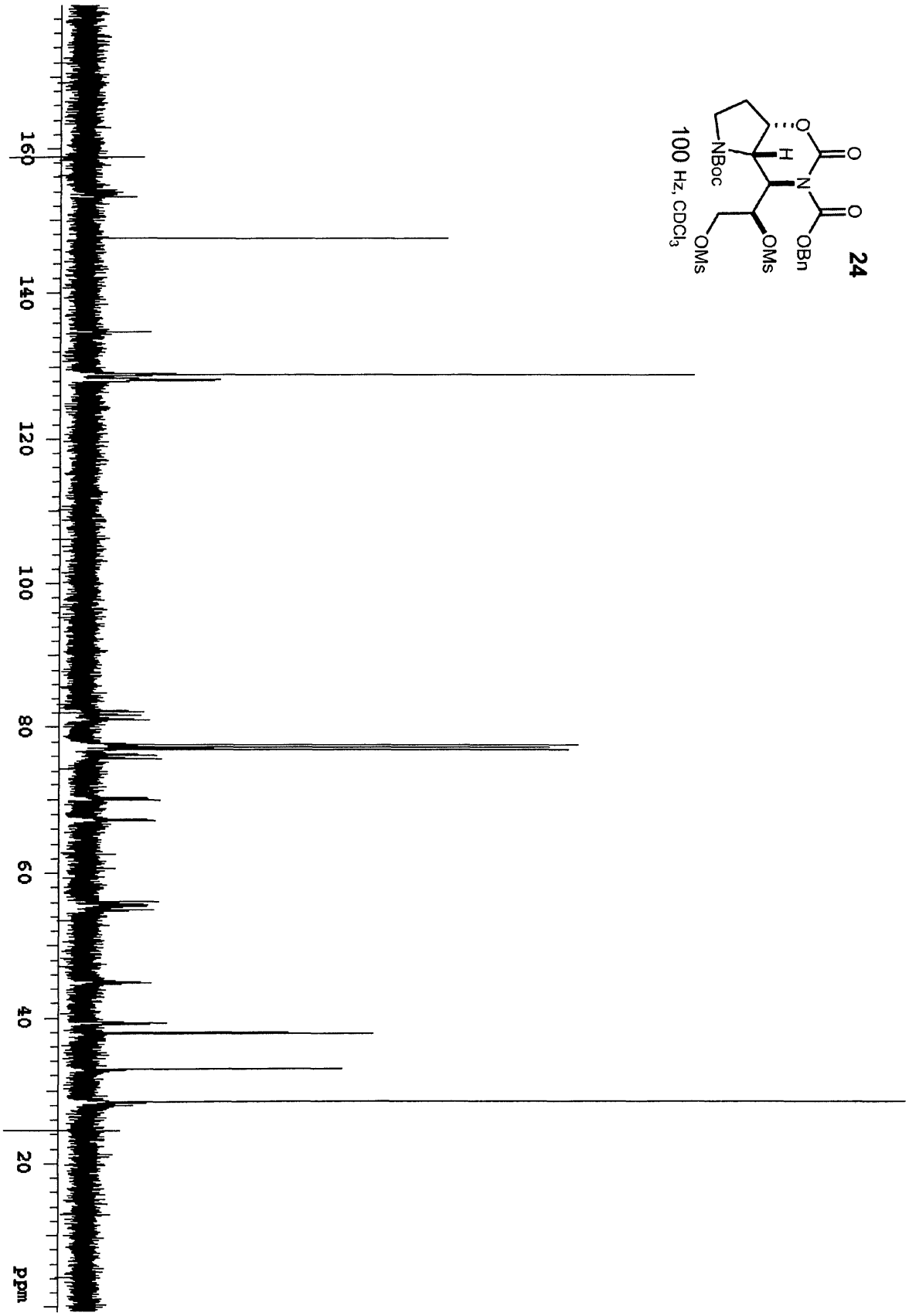

400 Hz, CD_3OD
NBoc
NH
OH
OH
3
ppm
0
1
2
3
4
5
6
7
8

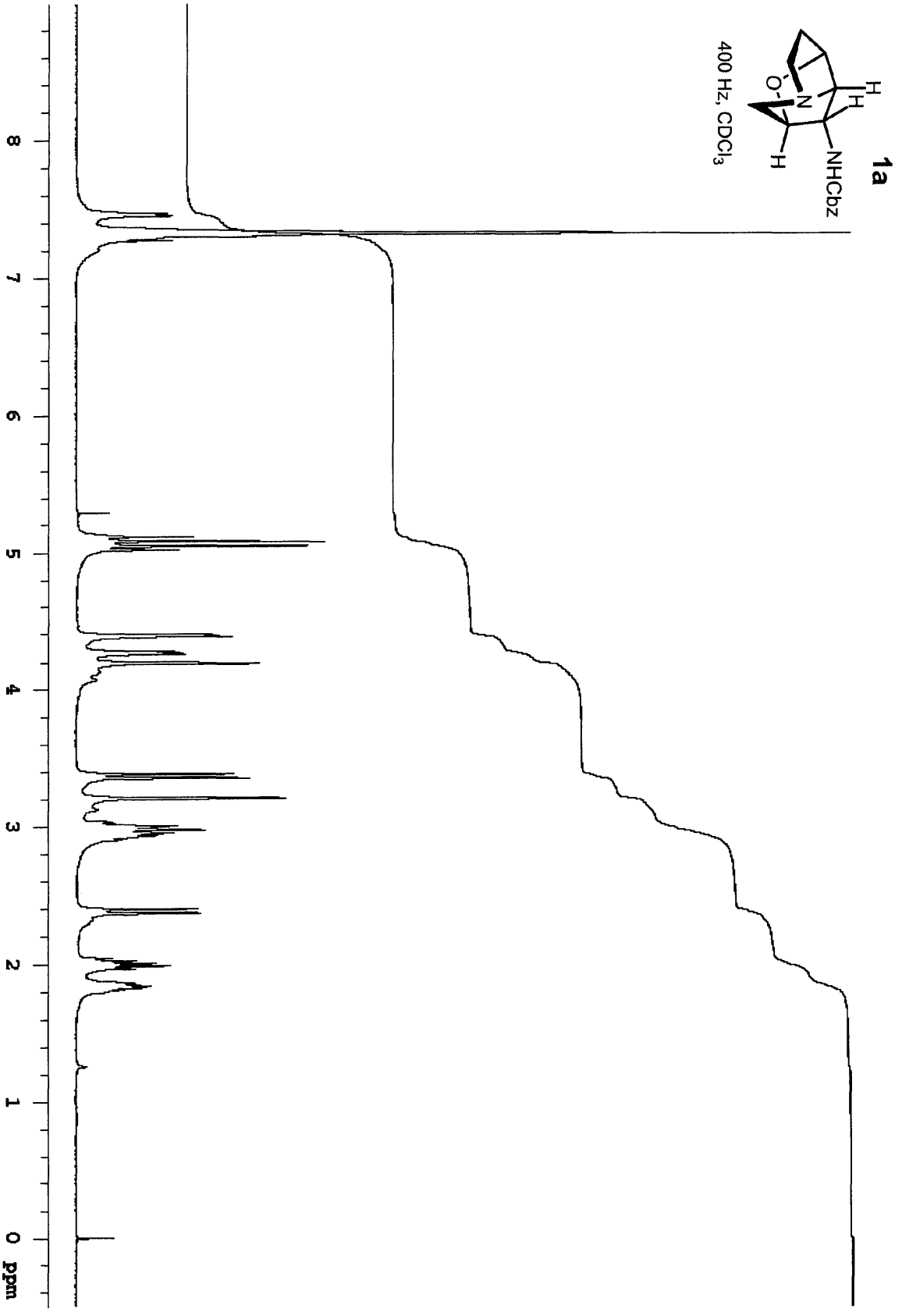

O
O
NH
H
OH
NBoc
OH
3
100 Hz, CD3OD
160
140
120
100
80
60
40
20
ppm

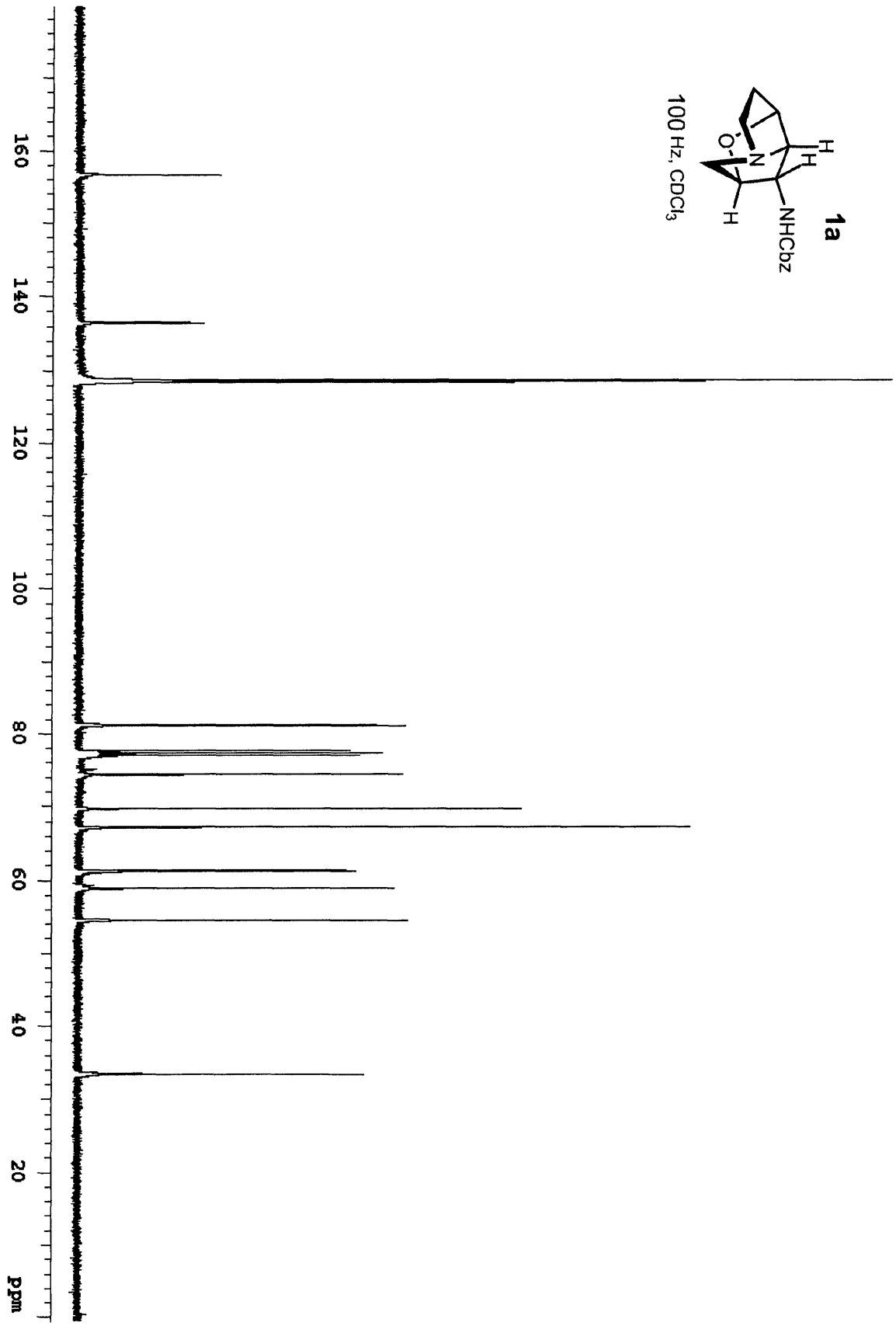

400 Hz, CDCl3
NBoc
NH
OMs
OMs
23
8
7
6
5
4
3
2
1
0 ppm

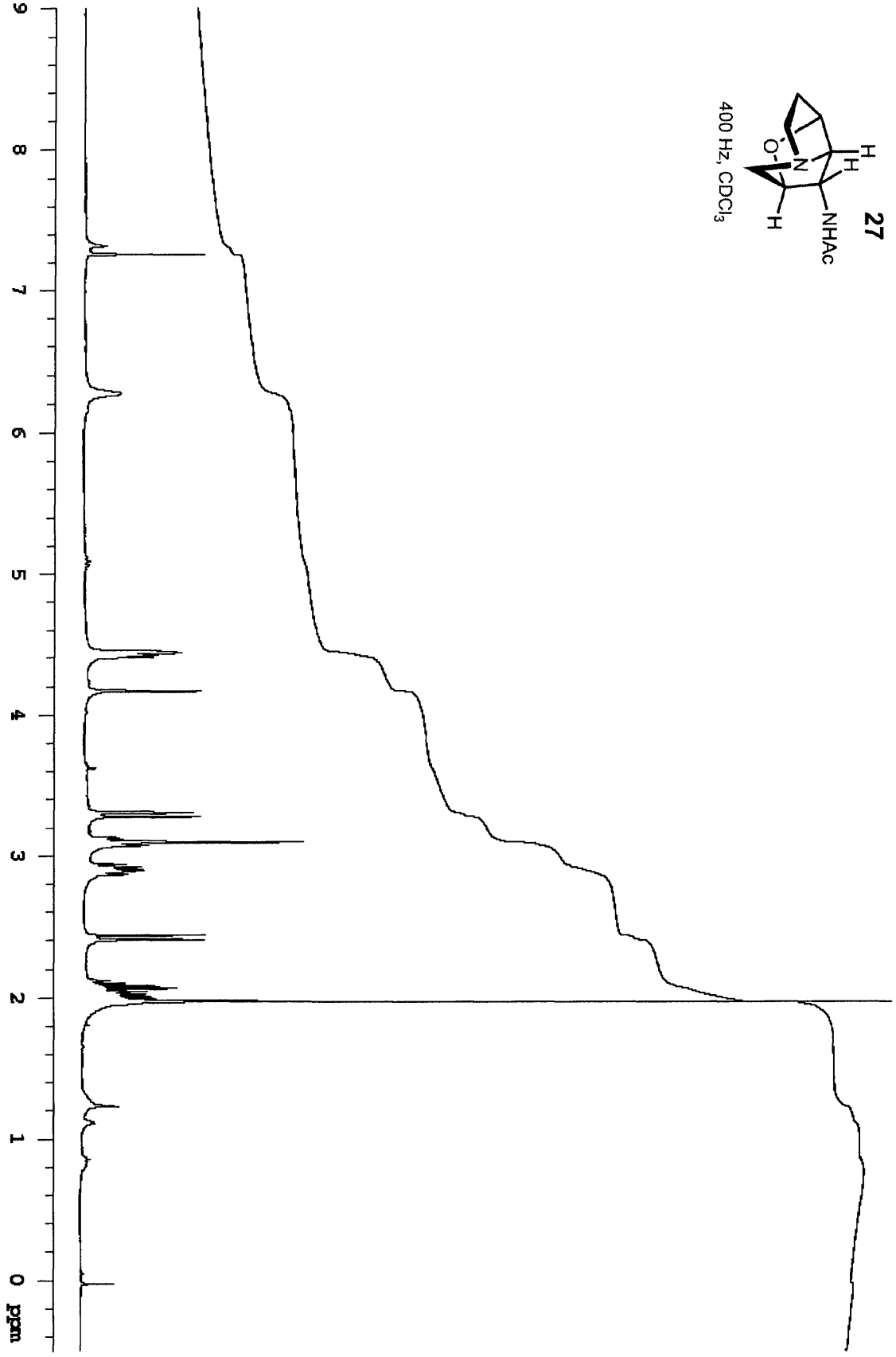

23
O
O
NH
H
OMs
NBoc
OMs
100 Hz, CDCl3
160
140
120
100
80
60
40
20
ppm


24
400 Hz, CDCl3
NBoc
OMs
OMs
OBn
ppm

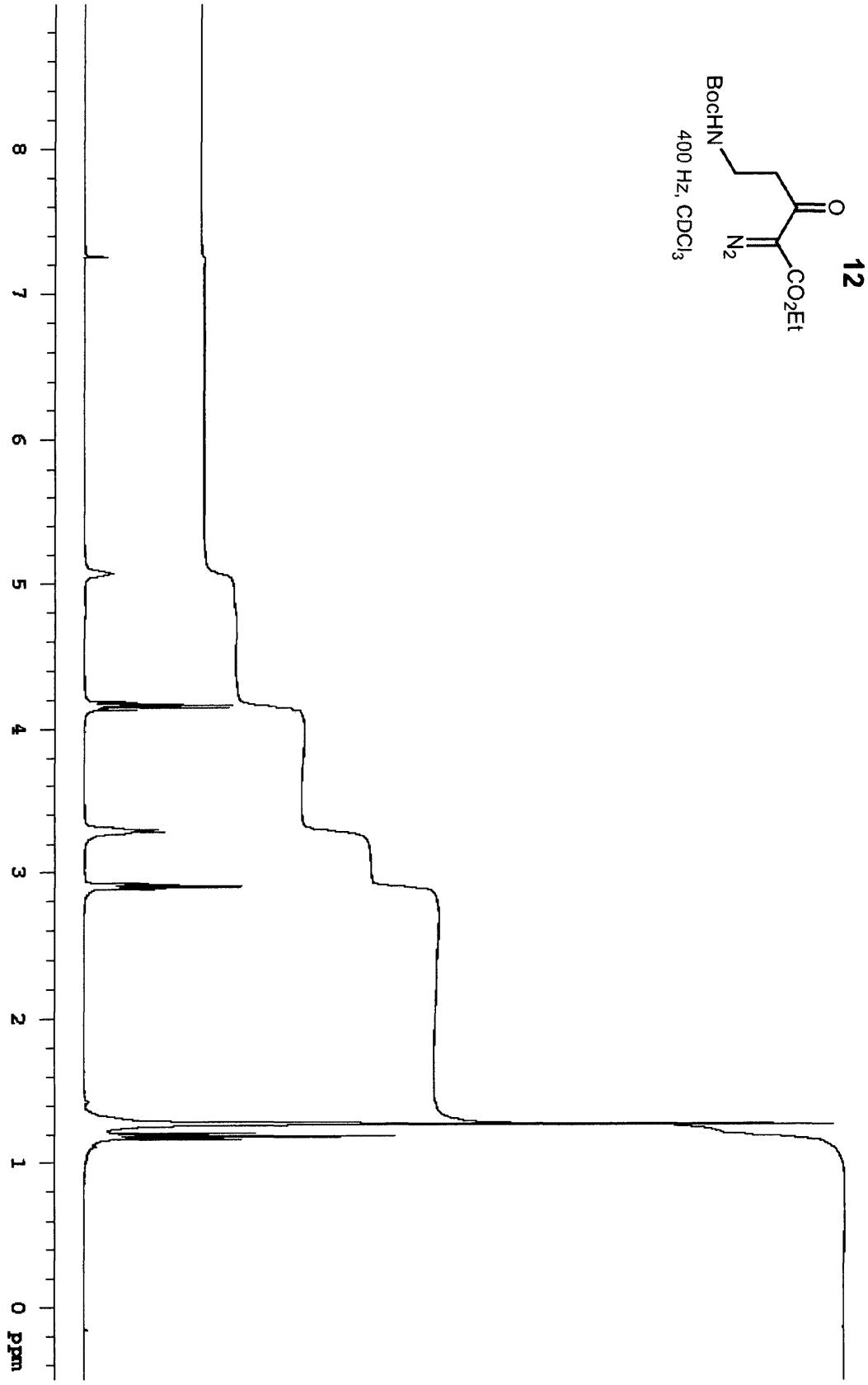

24
100 Hz, CDCl3
160
140
120
100
80
60
40
20
ppm

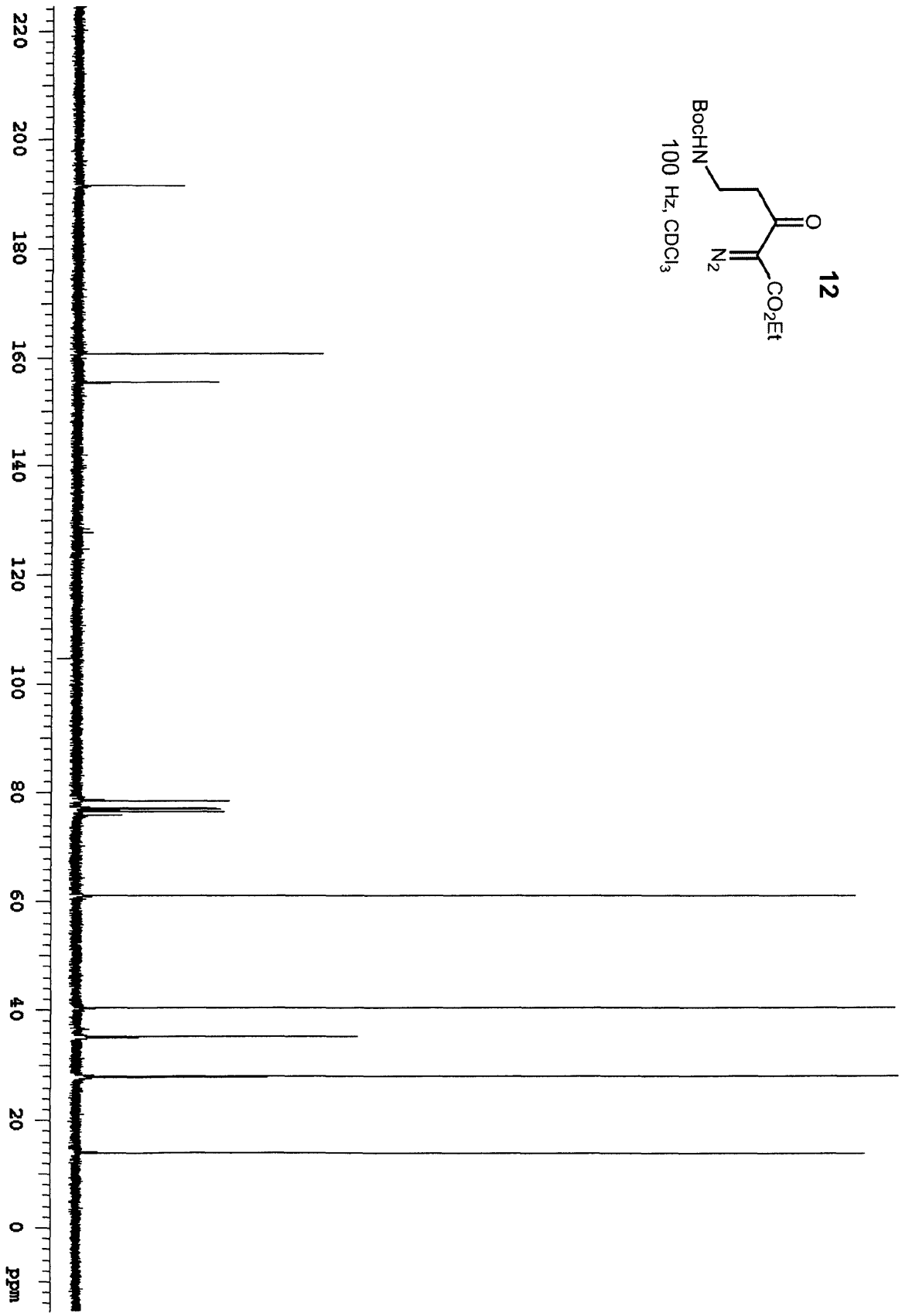

400 Hz, CDCl3
1a
NHCbz
H
H
H
O
N
8
7
6
5
4
3
2
1
0
ppm


100 Hz, CDCl3
1a
NHCbz
160
140
120
100
80
60
40
20
ppm


27
400 Hz, CDCl3
NHAc
H
H
H
O
N
ppm
0
1
2
3
4
5
6
7
8
9

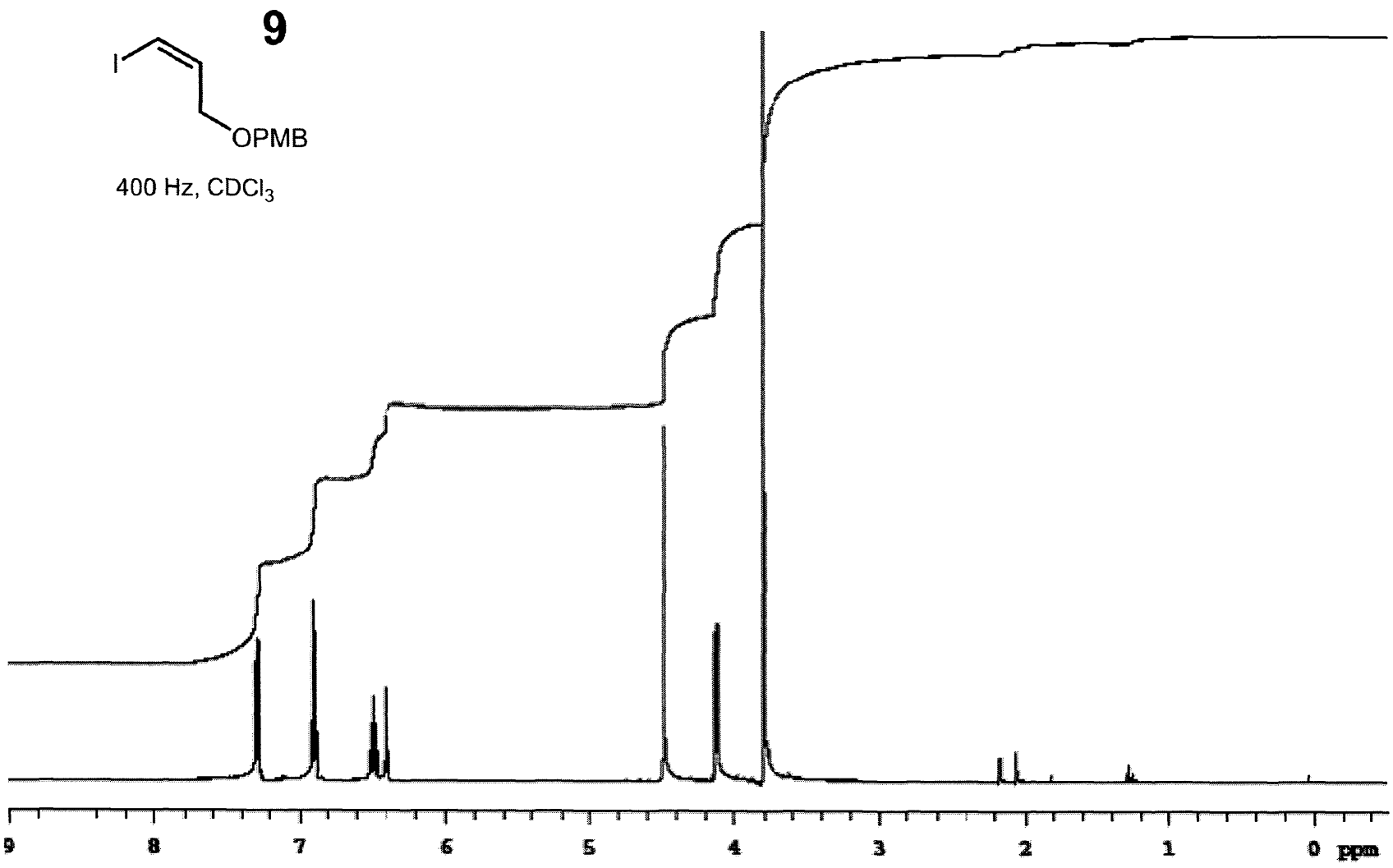
27
100 Hz, CDCl3
NHAc
H
H
H
N
O
180
160
140
120
100
80
60
40
20
ppm


12
BocHN
O
N2
CO2Et
400 Hz, CDCl3
8
7
6
5
4
3
2
1
0
ppm


BocHN
O
N2
CO2Et
12
100 Hz, CDCl3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Supporting Information For:

Chapter III: Studies Directed Toward the Asymmetric Total Synthesis of the Lolium Alkaloids Via Petasis Borono-Mannich Coupling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I
OPMB
400 Hz, CDCl3
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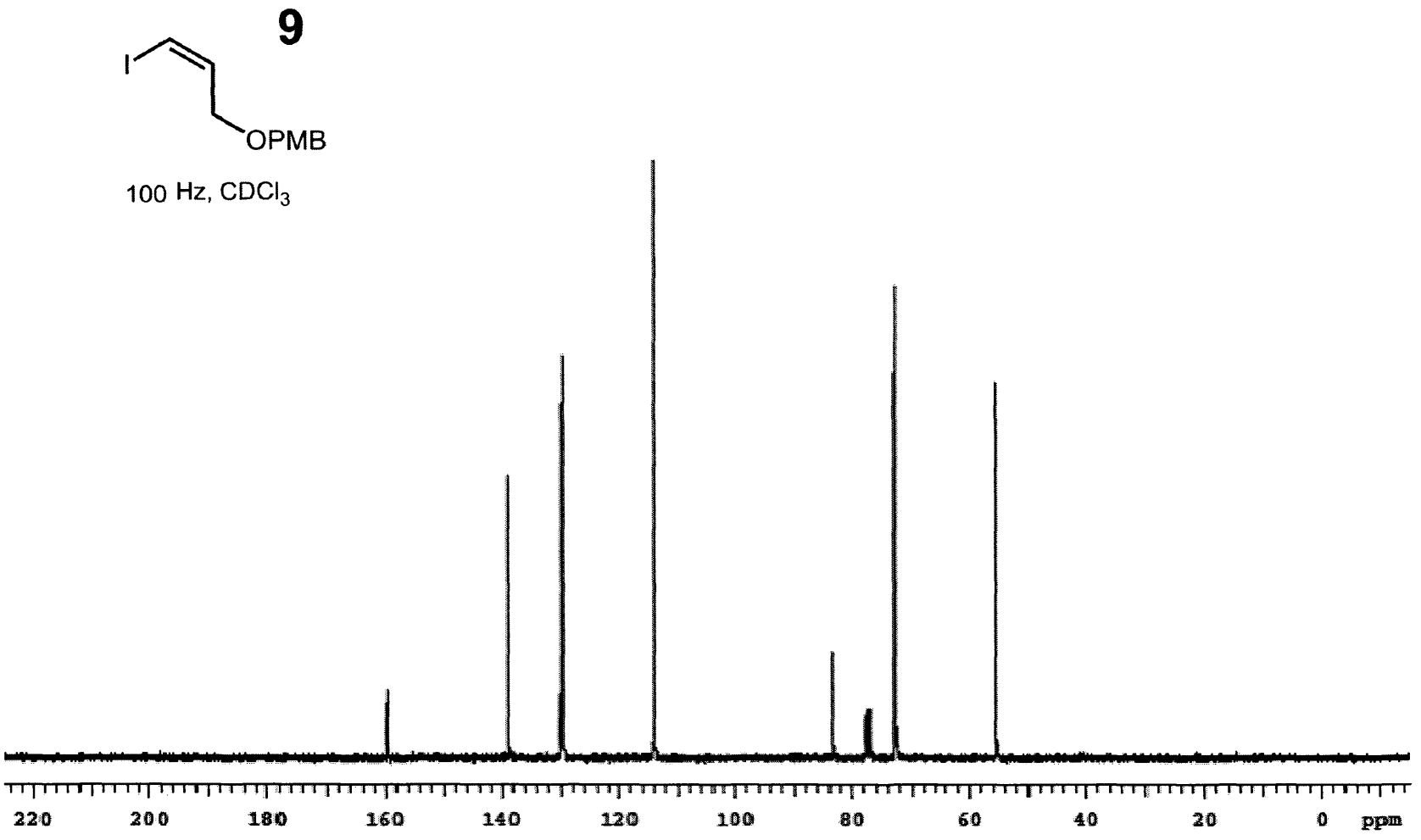
2
1
0
ppm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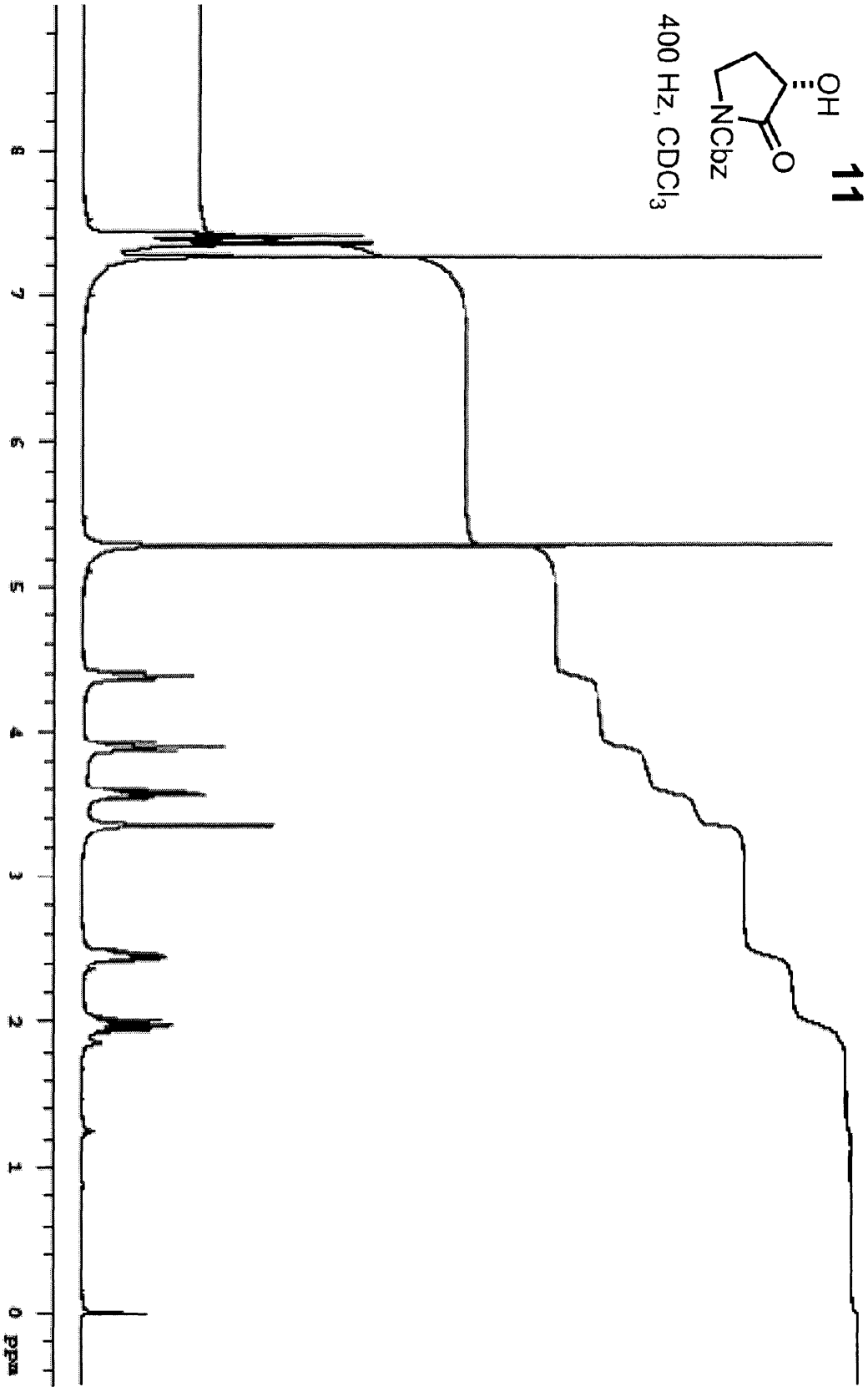
11
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NCbz
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400 Hz, CDCl3
ppm
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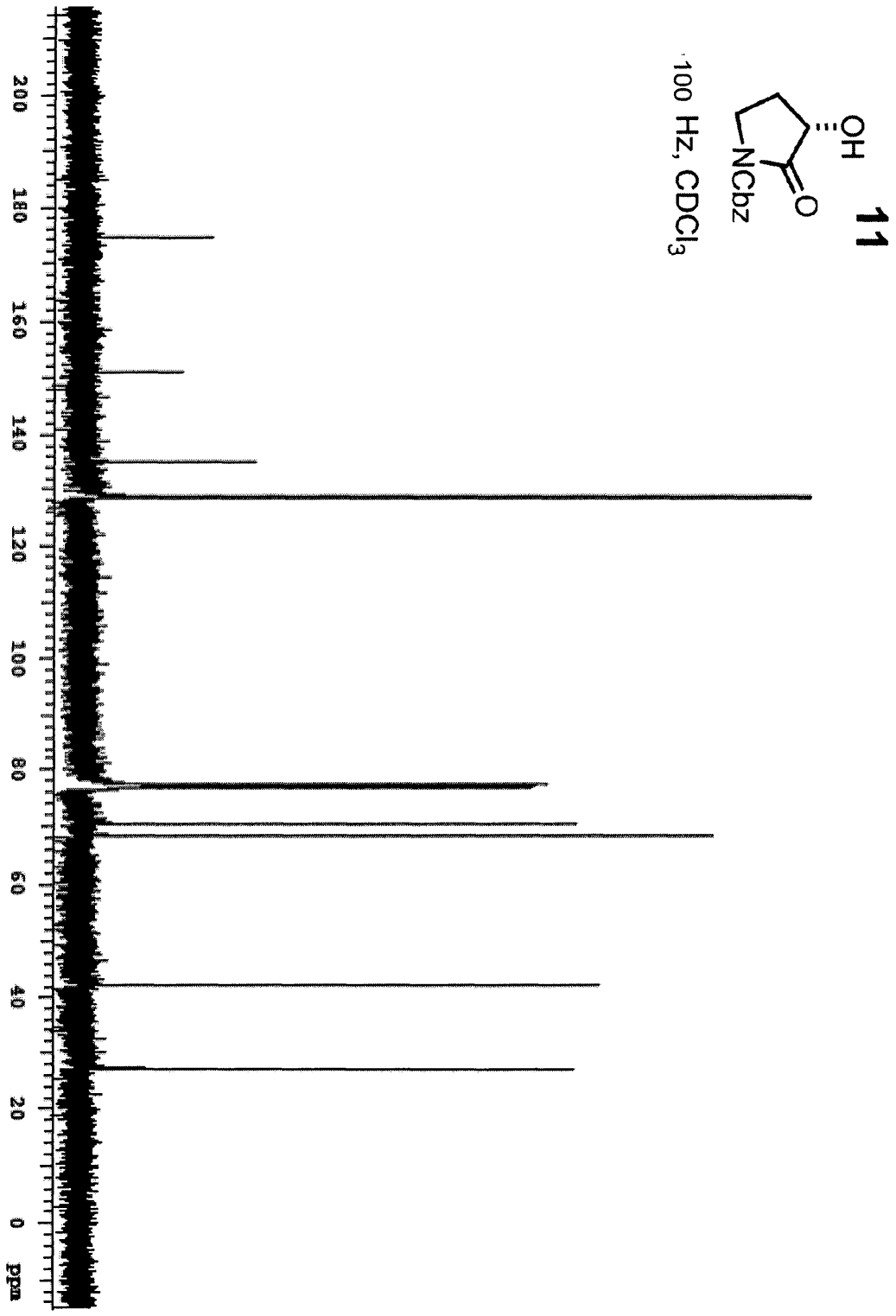
5
6
7
8


11
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NCbz
O
100 Hz, CDCl3
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40
20
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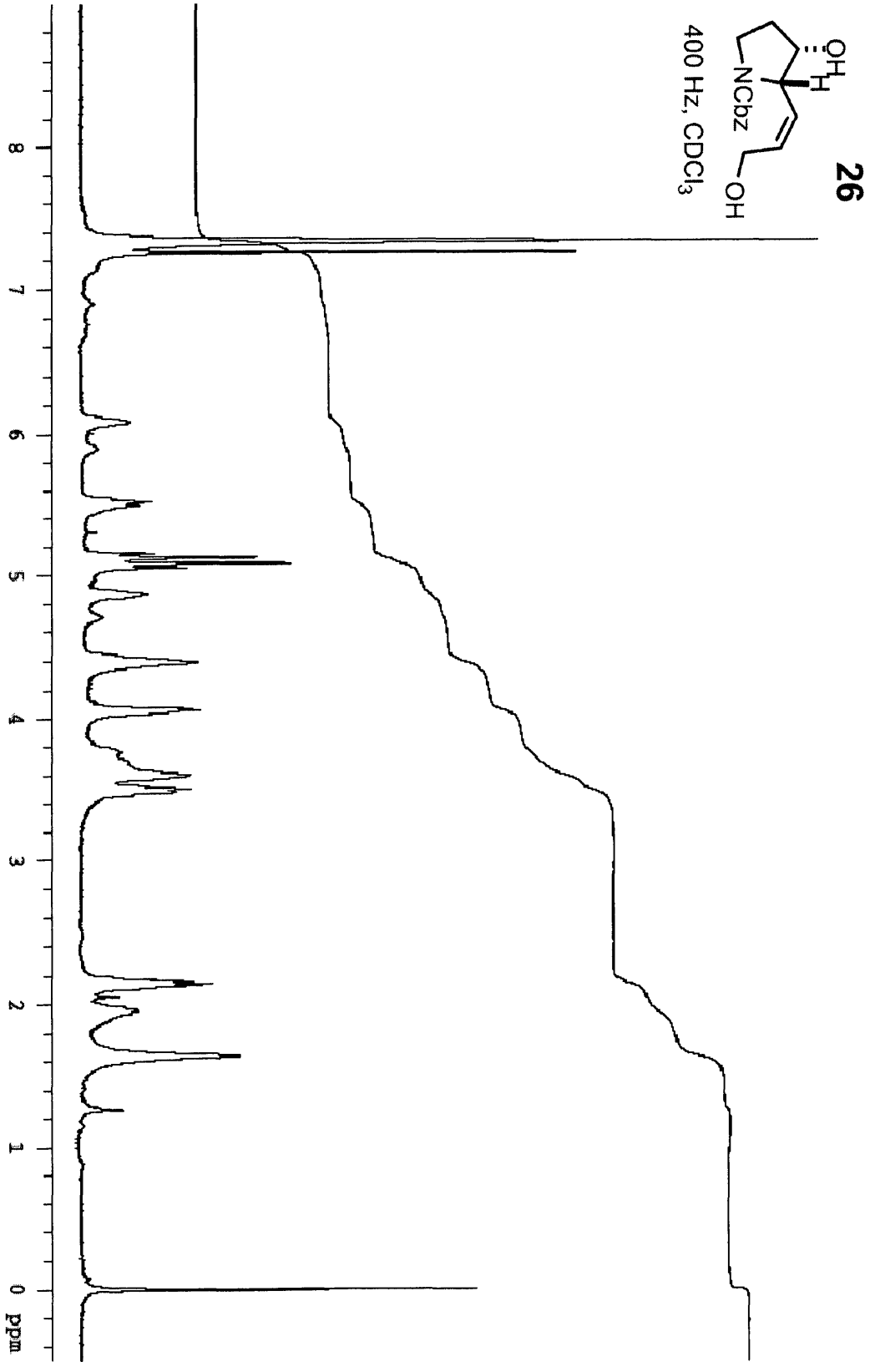
ppm


26
400 Hz, CDCl3
NCbz
OH
OH
H
8
7
6
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3
2
1
0
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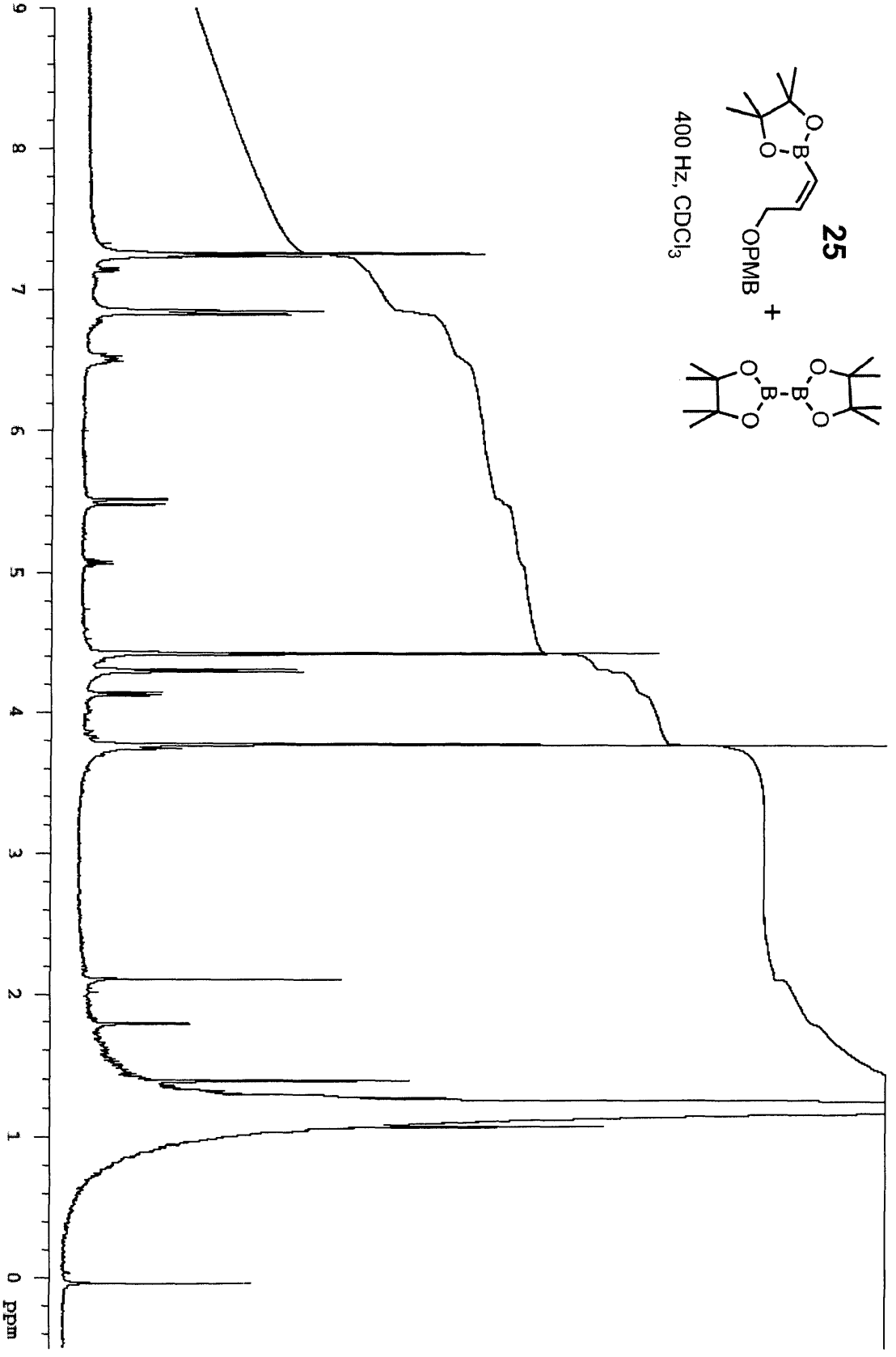
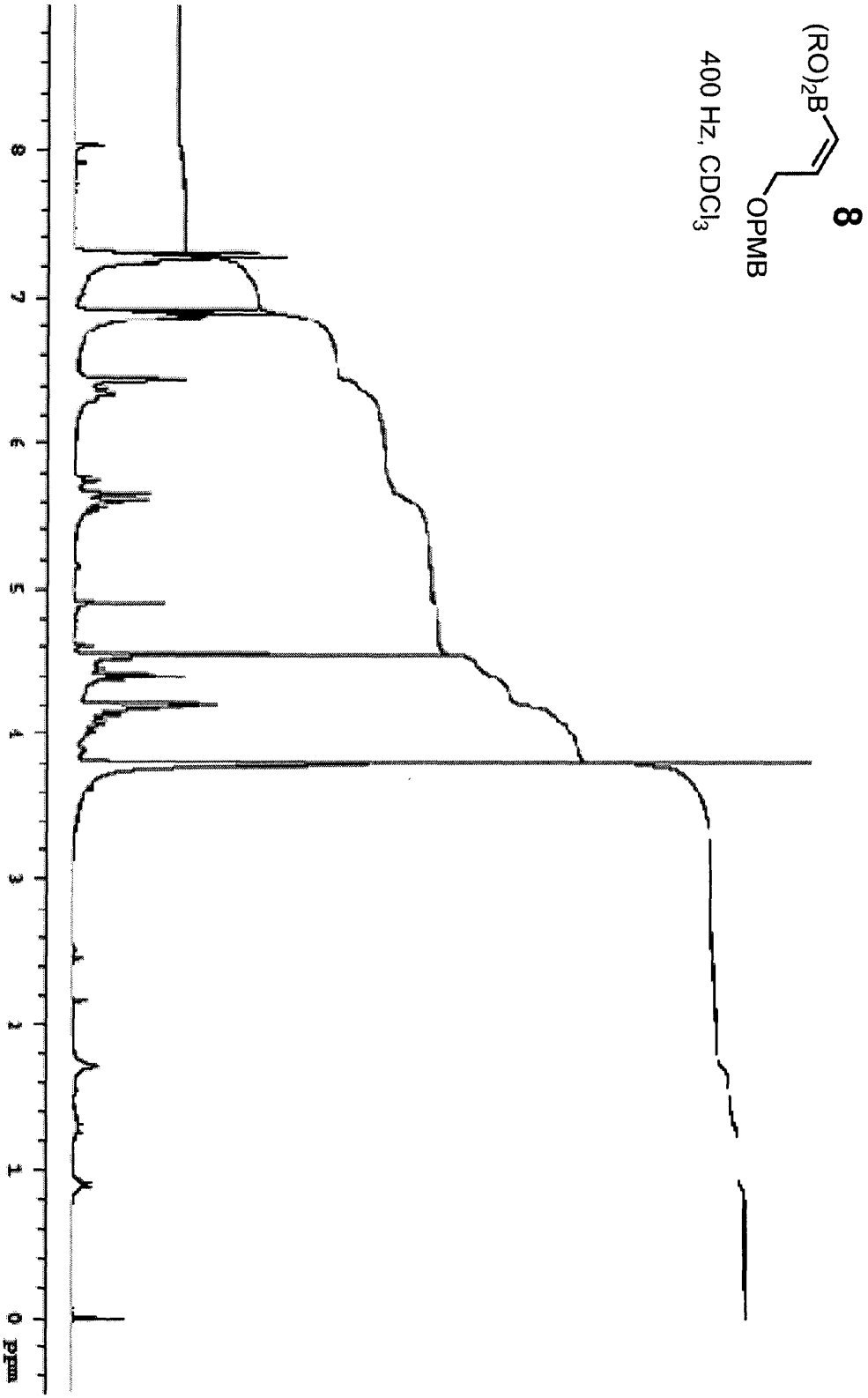

400 Hz, CDCl3
OPMB
25
+
9
8
7
6
5
4
3
2
1
0 ppm


(RO)2B
OPMB
8
400 Hz, CDCl3
ppm 0
1
2
3
4
5
6
7
8

VITA

Michael Todd Hovey, Jr.

M. Todd Hovey, Jr. was born in Virginia Beach, VA on April 22nd, 1988 to Carolyn and Michael Hovey. He graduated from Hayfield Secondary School in June 2006 and received his B.S. in Chemistry at The College of William and Mary in May 2010. In June 2010, the author began studies towards the degree of Master of Science under the tutelage of Professor Jonathan Scheerer. He defended his thesis little over a year later on July 14, 2011. In September 2011, he will be continuing his studies of organic chemistry at Northwestern University, working towards a Ph.D. His research areas of interest are synthetic methodology, natural product total synthesis, and physical organic chemistry.